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Cyclosporine Ophthalmic Emulsion 0.05% for the Treatment of Keratoconjunctivitis Sicca

FDA Advisory Committee Briefing Document

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1.0 EXECUTIVE SUMMARY

Based on 2 well-controlled Phase 3 clinical trials, cyclosporine ophthalmic emulsion 0.05% (tradename, RESTASIS™) is proposed for twice-daily (BID) treatment of moderate to severe keratoconjunctivitis sicca (KCS), commonly referred to as dry-eye disease. RESTASIS™ is recommended for patients with chronic disease: patients with a confirmed diagnosis of KCS that is inadequately controlled by conventional palliatives such as artificial tears and ointments.

Clinical Background. KCS can be severe, debilitating, and sight-threatening. Patients with moderate to severe KCS are constantly aware of their eyes; even blinking and bright light can cause pain. Their quality of life and their ability to function can be diminished because their eyes are frequently sore and irritated. Demographic studies indicate that KCS affects millions of people worldwide; up to 11% of people aged 30 to 60 years (Bjerrum, 1997) and up to 14.6% of people aged 65 years and older (Schein et al, 1997). Current treatment options for KCS are palliative, providing symptomatic relief without addressing the underlying mechanism of the disease.

Scientific Rationale. Research showing that KCS is a localized immune disease led to the choice of cyclosporine ophthalmic emulsion as an experimental therapy. The Sponsor's subsequent studies show that the 0.05% formulation improves the signs and symptoms of KCS and reduces the ocular inflammation and immune reactivity associated with the disease, providing significant therapeutic benefit. The 0.05% concentration was at least as effective as 0.1% cyclosporine emulsion, which also was evaluated in these studies. Both concentrations were safe and well tolerated.

Safety. In the Phase 2 and Phase 3 studies, 714 patients were exposed to concentrations of cyclosporine ophthalmic emulsion ranging from 0.05% to 0.4% for up to 3 months, and 0.05% to 0.1% for 6 months. Systemic exposure from topical administration of cyclosporine ophthalmic emulsion is nearly undetectable, and is thousands of times lower than the blood concentrations seen with oral cyclosporine treatment in rheumatoid arthritis and psoriasis patients. In the Phase 3 studies, blood concentrations of cyclosporin A for patients treated

with 0.05% cyclosporine ophthalmic emulsion were uniformly below the quantitation limit of 0.1 ng/mL, and there was no detectable drug accumulation in the blood.

Cyclosporine ophthalmic emulsion is well tolerated locally and does not have significant systemic effects. The most common adverse event following the use of 0.05% cyclosporine ophthalmic emulsion was ocular burning (16%). Other ocular adverse events reported by more than 3% (9/293) of patients receiving 0.05% cyclosporine emulsion in the Phase 3 studies (in order of decreasing incidence) were discharge, foreign body sensation, conjunctival hyperemia, stinging, irritation, and visual disturbance. Investigators did not consider any of these adverse events to be of serious concern.

No ocular infections were reported following administration of cyclosporine ophthalmic emulsion. Ocular flora evaluated in the Phase 2 study after 12 weeks of treatment showed a trend toward fewer bacterial species and fewer strains of organisms compared to baseline in cyclosporine-treated patients.

Efficacy. Two well-controlled Phase 3 clinical trials enrolled 877 patients with KCS, 671 of whom completed 6 months of treatment with 0.05% cyclosporine emulsion, 0.1% cyclosporine emulsion, or vehicle. Based on a factor analysis across all efficacy parameters at baseline, an

Responders were defined as patients whose

In each study at month 6, significantly more patients responded to treatment with cyclosporine ophthalmic emulsion (43% to 50%) than to treatment with vehicle (29% to 31%). (P = 0.014 and 0.012 in studies 002 and 003, respectively.)

With respect to the individual efficacy variables, virtually all showed statistically significant improvements from baseline within each treatment group in each study. At month 6, among the statistically significant improvement favoring cyclosporine versus vehicle was found in study 002 for corneal staining (P = 0.008) and in study 003 for Schirmer with anesthesia (P < 0.001). Marginal significance favoring

cyclosporine was found for Schirmer with anesthesia in study 002 (P = 0.066) and for REFRESH® use in study 003 (P = 0.087).

Additional specialized laboratory tests performed following 6 months of treatment showed that cyclosporine ophthalmic emulsion:

Risk-Benefit. Use of cyclosporine ophthalmic emulsion results in improvements in the signs and symptoms of KCS and a reduction in ocular surface inflammation. Additionally, the BID dosing and decreased need for artificial tears make cyclosporine emulsion a more tolerable treatment for patients who are used to instilling artificial tears very frequently. These benefits significantly outweigh the minimal risks associated with this treatment. The favorable risk/benefit ratio is further reinforced by the lack of satisfactory alternative therapies for these patients.

2.0 KERATOCONJUNCTIVITIS SICCA: BACKGROUND AND OVERVIEW

This briefing document presents the efficacy and safety data supporting approval of 0.05% cyclosporine ophthalmic emulsion (tradename, RESTASIS™) for the treatment of moderate to severe keratoconjunctivitis sicca (KCS). Currently there is no available effective pharmacologic treatment for people with chronic dry-eye disease. The background and overview section provides information on KCS, currently available treatments, and the rationale for the use of cyclosporine ophthalmic emulsion for this condition.

2.1 NATURE OF KERATOCONJUNCTIVITIS SICCA AND NEW CONCEPTS

2.1.1 SYMPTOMS AND DEMOGRAPHICS

KCS, commonly referred to as dry eye, is a disease affecting the ocular surface, the tear film, and related ocular tissues and organs. Patients with dry-eye disease typically complain of ocular discomfort and a constant awareness of their eyes, including symptoms of a dry, gritty feeling often accompanied by foreign body sensation. Symptoms often become worse as the day progresses. Burning and irritation, photophobia, blurred vision, and gradual contact lens intolerance can occur (Lubniewski and Nelson, 1990). Some patients are unable to cry irritative or emotional tears (Lubniewski and Nelson, 1990). Depending on the duration and severity of disease, damage to the ocular surface may be present and those with chronic, uncontrolled disease have an increased risk of ocular infections (Lemp and Chacko 1997; Lubniewski and Nelson, 1990; Mackie and Seal, 1984; Omerod et al, 1988; Seal, 1985). Complications of severe dry-eye disease also include corneal melting located either peripherally or paracentrally.

Dry-eye disease can be severe, debilitating, and sight-threatening. Patients with moderate to severe KCS are constantly aware of their eyes; even blinking and bright light cause pain. Their quality of life and their ability to function can be diminished because their eyes are frequently sore and irritated. They are unable to tolerate dry climates and air conditioning and need to wear unsightly goggles. They, along with their physicians, are further frustrated because there is no satisfactory treatment available.

Demographic studies indicate that KCS of varying severity affects millions of people worldwide; up to 11% of people aged 30 to 60 years (Bjerrum, 1997) and up to 14.6% of people aged 65 years and older (Schein et al, 1997). The incidence of KCS increases with age (McCarty et al, 1998; Patel and Farrell, 1989). Extrapolating from the Schein sample of elderly Americans with dry-eye symptoms to the US population aged 65 years and older, an estimated 4.3 million older Americans suffer from symptoms of ocular irritation often or all the time (Schein et al, 1997). Women are more likely to report severe symptoms of dry eye than men (McCarty et al, 1998), but new epidemiology studies show that the prevalence among men and women is similar (Schein et al, 1997). Approximately 15% (Hikichi et al, 1995) of patients visiting ophthalmic clinics report dry-eye symptoms.

2.1.2 TYPES OF KCS

According to the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, dry eye may be classified into 2 types—evaporative and tear-deficient or, more precisely, aqueous-deficient dry eye (Lemp, 1995). In the dry-eye category characterized by excessive tear evaporation, the quantity of aqueous fluid from the lacrimal glands is normal and the tear abnormality is due to increased tear evaporation. Evaporative dry eye may be associated with other periocular diseases and disorders, including blepharitis, meibomian gland disease, ocular mucin deficiencies, blinking disorders, proptosis associated with thyroid disease, and structural abnormalities of the lids and eye causing exposure of the ocular surface.

The dry-eye category characterized by aqueous deficiency is further divided into patients with Sjögren's syndrome (a systemic autoimmune disease) and those with KCS in the absence of any related systemic disease (non-Sjögren's KCS). Recent data show that immune-based inflammation of the ocular surface contributes to both disorders (Power et al, 1993; Stern et al, 1998). The histopathological changes of the lacrimal gland in the patients with Sjögren's syndrome consist of lymphocytic infiltration leading to atrophy and destruction of glandular function (Sanders and Graham, 1986). Most cases of lacrimal gland insufficiency, however, cannot be attributed to Sjögren's syndrome. Williamson et al (1973) and Damato et al (1984) have described the presence of a lymphocytic infiltrate in the lacrimal glands of non-Sjögren's KCS patients and suggest that atrophy of the lacrimal gland

in these patients represents a chronic, progressive inflammatory local process in the absence of systemic autoimmune disease.

2.1.3 NEW CONCEPTS IN THE PATHOPHYSIOLOGY OF KCS

Over the past 3 to 5 years, significant advances have been made in our understanding of the pathophysiology of KCS. In the normal individual, tear secretion is controlled via a neural reflex. Stimulation of the ocular surface induces afferent nerve traffic to the central nervous system, where it is integrated and results in efferent nerve traffic (both sympathetic and parasympathetic) to the lacrimal glands (main and accessory). In the lacrimal glands, neural stimulation produces cellular water movement and tear secretion. Under normal conditions in the eye, trafficking immune cells, such as T cells, migrate through the lacrimal glands and ocular surface tissues in an inactivated state as part of the body's routine immunovigilance. These immunovigilant T cells undergo a normal apoptotic cell death as they exit the glands and travel toward local lymph nodes (Gao et al, 1998). Under these conditions, the ocular apparatus is in a state of immunoquiescence and homeostasis is sustained.

In dry-eye patients, the disease can stem from multifactorial etiologies that result in a common immune-based inflammation of the lacrimal glands and ocular surface. There appear to be 2 distinct mechanisms that can trigger dry-eye disease.

First, a localized autoimmune event occurs in the ocular tissues against a purported backdrop of genetic/hormonal predisposition. The loss of normal hormonal support to the lacrimal tissues results in a local environment that facilitates or permits initiation of inflammatory processes. Neurogenic stimulation is thought to play a role in upregulating inflammation in this first mechanism.

Second, chronic physical irritation to the ocular surface may occur, as a result of environmental stress such as, wind, low humidity, or increased abrasive forces from blinking over an ocular surface with an inadequate tear film. Initiation of ocular surface inflammation can occur through deficiencies in any one or more of the 3 tear component layers. For example, irritation-induced decreases in goblet cell density and epithelial mucin production result in alterations of cell status in terminal differentiated ocular epithelial cells (Pflugfelder,

1997). Subsequently, the altered expression and/or activity of epithelial cell cytokines initiate ocular inflammation. The result of this irritative inflammatory response is cytokine-driven immune activation and T cell homing. Biopsy specimens from patients whose disease etiology stems from predominantly an irritative mechanism would, therefore, resemble those with severe local and/or systemic autoimmunity. Thus, inflammation from chronic physical irritation may develop without predisposing immunoreactivity.

Either etiology results in ocular surface inflammation with immune involvement, which produces signs and symptoms that are indistinguishable in the patient. Whether irritation of the ocular surface is the primary initiating event or the secondary result of a localized immune event, the irritated ocular surface is key to perpetuating the disease. Ocular irritation, inflammation, and the resultant abnormal tear film all interact to create the signs and symptoms of dry-eye disease.

2.1.4 RECENT EVIDENCE TO SUPPORT THE IMMUNE-BASED INFLAMMATORY ETIOLOGY OF KCS

The underlying immune-based inflammatory component of KCS, with and without Sjögren's syndrome, has been verified in specialized laboratory tests conducted in untreated patients with KCS. Baseline data from the Sponsor's Phase 3 clinical trials specialized laboratory tests

have shown elevated levels of:

, whereas low levels have been reported in normal subjects (Baudouin et al, 1997; Jones et al, 1994).

2.2 CURRENT TREATMENTS FOR KERATOCONJUNCTIVITIS SICCA

Although dry-eye disease is a chronic process for which there is currently no cure (Lemp and Chacko, 1997), various treatment modalities have been used to help patients manage their disease, including palliatives, devices, and surgery. None of these treatments addresses the immune-based inflammatory component of KCS.

2.2.1 PALLIATIVES AND PHARMACOTHERAPIES

Supplementation of tears with the use of tear substitutes has been the mainstay of relief for dry-eye disease. Tear substitutes are available in both preserved and nonpreserved formulations. Preserved artificial tears are formulated to help those with mild disease who require relatively infrequent instillation of the product, while nonpreserved formulations are useful for those with more severe disease and compromised ocular surfaces. Sustained-release inserts and gels reduce the need for frequent instillation, but many cause blurring and discomfort and are difficult to use. Lubricating ointments are helpful in providing relief at night, when their tendency to blur vision is not as critical (Lemp and Chacko, 1997).

In the absence of other practical and effective treatments, topical corticosteroids have been used as a short-term treatment option. Their well known adverse effects, such as increased intraocular pressure, increased risk of cataract formation, decreased wound healing, and exacerbation of infection, have limited their use as long-term therapy (Lemp and Chacko,

1997). In a retrospective, noncomparative series of 21 cases, use of topical nonpreserved methylprednisolone for 2 weeks has been reported to be effective in the treatment of KCS, further supporting the inflammatory nature of the disease (Marsh and Pflugfelder, 1999).

Pilocarpine hydrochloride also has been used experimentally. Oral pilocarpine hydrochloride (9 mg/day, 3 times daily), which stimulates lacrimal gland tear production, has been studied in 21 patients with Sjögren's syndrome, 5 of whom showed subjective dry-eye improvement (Takaya et al, 1997).

2.2.2 DEVICES

Numerous types of devices have been used to help patients with dry-eye disease, including goggles, moisture chambers, and humidifiers. The use of bandage contact lenses is beneficial for patients with severe ocular surface disease and intractable filamentary keratitis that does not respond to treatment, but has serious risks of infection and corneal ulcers (Lemp and Chacko, 1997). Temporary devices are available for occluding the puncta to block tear drainage and often are used to determine if a patient will be helped by permanent punctal occlusion. However, each of these devices has its own set of unique complications.

2.2.3 SURGERY

Cautery and the argon laser (argon laser punctoplasty) are used for permanent punctal occlusion, and lid surgery can correct congenital or acquired lid abnormalities causing dry eye (Lubniewski and Nelson, 1990). In cases of severe ocular surface disease, tarsorrhaphy decreases the exposed ocular surface, thereby decreasing tear evaporation (Lemp and Chacko, 1997).

2.3 RATIONALE FOR TREATMENT WITH CYCLOSPORINE OPHTHALMIC EMULSION

Cyclosporine ophthalmic emulsion is expected to benefit KCS patients through its ability to modulate the immune reactivity and inflammatory processes that are now known to underlie dry-eye disease (Stern et al, 1998). Within the ocular surface, cyclosporine ophthalmic emulsion acts as:

- an immunomodulator
- an anti-inflammatory agent
- a direct inhibitor of pathological epithelial apoptosis.

2.3.1. IMMUNOMODULATION

Cyclosporine is effective because of its local action on the immune system and not because of effects resulting from systemic absorption (Power et al, 1993), since blood cyclosporin A (cyclosporine) concentrations are far below levels required for systemic immunosuppression (study reports PK-96-018, PK-98-109, and PK-98-112). This local effect has been termed immunomodulatory.

This local immunomodulatory effect is rendered by the unique and selective effect of cyclosporine. T lymphocyte activation is selectively inhibited and, therefore, permits adaptive, specific recognition of pathogens. Granulocytes, monocytes, and macrophages are less sensitive to cyclosporine, and therefore continue to perform their immune/physiological processes such as phagocytosis, digestion, and metabolism (Kahan, 1989).

Dry-eye patients, with or without systemic autoimmune disease, exhibit chronic inflammation in the lacrimal gland and ocular surface. Immunohistochemical studies have demonstrated that infiltrating lymphocytes within these tissues consist primarily of CD4 (T-helper) cells (Pepose et al, 1990; Pflugfelder et al, 1986). T-helper cells play an important role in the immune response and also in the inflammatory response through cytokine synthesis. Cyclosporine specifically affects T-helper cells by inhibiting their activation and ability to recruit additional T cells to an immune-active site.

Another effect of cyclosporine is to block the production of IL-2, a key cytokine needed for regulation and amplification of an immune event (Borel et al, 1996). Through a decrease in IL-2 and other cytokines, cyclosporine prevents the recruitment of additional T cells and prevents the activation of otherwise vigilant T cells within the ocular tissue. Cyclosporine also inhibits activation of nuclear factor NF-κB, which is involved in the regulation of immune and pro-inflammatory cytokine response genes such as TNF, IL-1, and IL-8 (Boss et

al, 1998; Meyer et al, 1997). Inhibition of cytokine secretion by cyclosporine prevents the amplification of immune reactivity and, indirectly, the resulting inflammation.

As an immunomodulating agent, cyclosporine has been shown to break the cycle of immune reactivity underlying the disease both in human dry-eye patients (Power et al, 1993) and in dogs with chronic, idiopathic dry eye disease (Kaswan et al, 1989; Stern et al, 1998). Topical ophthalmic cyclosporine reduces lacrimal gland lymphocytic infiltrates and improves tear production in KCS patients with or without Sjögren's syndrome (study report 192371-001; Drosos et al, 1986; Laibovitz et al, 1993; Power et al, 1993; Stern et al, 1998) and in dogs with KCS (Kaswan et al, 1989; Kaswan and Salisbury, 1990; Morgan and Abrams, 1991; Olivero et al, 1991). Power and associates have further demonstrated that patients with dry-eye disease (secondary Sjögren's disease) are undergoing continued immune reactivity by the presence of significantly more CD4+ cells (T helper/inducer cells) than age- and sex-matched controls. Following treatment with topical cyclosporine, there was a significant reduction in the number of CD4+ cells in both the conjunctival epithelium and substantia propria, indicating reduced immune reactivity (Power et al, 1993).

2.3.2 ANTI-INFLAMMATORY ACTIVITY

Cyclosporine regulates inflammation within the tissues of the ocular surface by inhibiting ICAM-1 expression on endothelial cells (Oran et al, 1997). Expression of this protein is critical to allow migration of lymphocytes through the blood vessel wall and into the substantia propria and conjunctival epithelium. CD11a is upregulated during activation of human lymphocytes and, with its ligand ICAM-1, plays an important role in cell-to-cell interactions and cell migration in inflammation (Dustin and Springer, 1988; Wakefield et al, 1992). Thus, downregulation of endothelial cell ICAM-1 by cyclosporine inhibits migration of inflammatory cells into the tissue.

Cyclosporine also has a direct anti-inflammatory action mediated by its inhibition of phosphatases. Phosphatases are a ubiquitous class of enzymes involved in a wide range of metabolic processes such as cell proliferation. Cyclosporin A inhibits the serine/threonine phosphatase, calcineurin (Florio et al, 1996), prohibiting the proliferation of inflammatory cells and subsequent inflammation within the ocular surface and lacrimal glands.

2.3.3 MODULATION OF PATHOLOGICAL APOPTOSIS

Some of the pathological changes seen in autoimmunity are related to pathological alterations in the apoptotic state of the tissues. The stability of secretory acinar epithelial cells in normal lacrimal glands is ensured by factors such as Bcl-2 anti-apoptotic cell survival factor, RB-protein (Retinoblastoma protein, dephosphorylated, maintains terminal differentiation), and circulating androgens (inhibit inflammation). As inflammatory induction of acinar cell death progresses, the secretory capacity of the glands is compromised.

Biopsy tissues from spontaneous, chronic idiopathic dry-eye dogs have shown pathological changes in apoptosis of lacrimal acinar and conjunctival epithelial cells (Gao et al, 1998). In humans, conjunctival biopsies from KCS patients have shown an abnormal decrease in the rate of apoptosis for infiltrating lymphocytes (Smith et al, 1999).

In ocular surface models of wound healing, evidence shows that the corneal epithelium undergoes increased pathological apoptosis (Wilson et al, 1996b). Modulators of apoptosis include the *Fas* system (*Fas* and *Fas* ligand [CD95]) and the CD40 system (CD40 and CD40 ligand), both as membrane-bound and soluble proteins (Ren and Wilson, 1996; Wilson et al, 1996a, 1996b). Cyclosporine has been shown to inhibit apoptosis directly in several cell types, including neurons, by binding to and preventing the opening of a mitochondrial permeability transition pore (Tatton and Chalmers-Redman, 1998).

Thus, cyclosporine's 3 modes of action in ocular tissue—as an immunomodulator, anti-inflammatory, and anti-apoptotic—make it a good candidate for the treatment of KCS.

3.0 PHASE 3 STUDY DESIGN AND ENROLLED PATIENT POPULATION

3.1 CLINICAL EVALUATION OF KERATOCONJUNCTIVITIS SICCA

Characterization of KCS is difficult for clinicians for several reasons:

- No single objective or subjective endpoint is specific for diagnosing dry-eye disease.

- A substantial portion of the disease is symptomatic; patients describe their subjective experiences uniquely (eg, eyes are scratchy, itchy, or dry).
- Objective signs and subjective symptoms often do not correlate.
- Standard clinical tests are only indirect assessments and do not measure the underlying inflammatory and immune-mediated pathology of dry-eye disease.
- The patient's physical environment (eg, weather, air conditioning) can acutely affect the ocular surface, changing objective and subjective assessments of the dry-eye condition.

Because of these challenges, the Sponsor has developed study approaches that contribute to the clinical understanding of this disease and its evaluation. These include the use of standard tests, a newly developed patient questionnaire, and a factor analysis that identifies key components contributing to the disease.

Standard tests used in clinical practice and additional tests used by the Sponsor in the Phase 3 clinical trials are described in the following section (3.1.1) and the analysis method (factor analysis) is described in Sections 3.2.7 and 4.1.1.

3.1.1 OBJECTIVE TESTS

Objective tests refer to assessments that are conducted and evaluated by the physician and/or clinical staff.

3.1.1.1 Staining

To assess damage to the ocular surface, staining techniques are used to evaluate both the cornea and the conjunctiva. In progressive dry-eye disease, the absence of ocular lubrication results in increased abrasive forces affecting the ocular surface, particularly the cornea. Because of the cornea's role in vision, evaluation of corneal pathology due to dry-eye disease is a particularly important assessment. The cornea is typically stained with fluorescein (Lemp, 1995; Lemp and Chacko, 1997), which stains areas of denuded epithelium and compromised epithelial junctions (punctate staining). Decreases in corneal staining scores from baseline are considered indicative of improved corneal health.

Historically, rose bengal stain has been used to assess conjunctival pathology (Feenstra and Tseng, 1992). However, no commercial liquid preparation of rose bengal stain was available at the time of Phase 3 study initiation and there was a concern that rose bengal strips, which require the addition of a solution and further manipulation, could not be used uniformly in a large, multicenter clinical trial. Therefore, a new conjunctival stain, lissamine green, which also causes less patient discomfort than rose bengal (Lemp, 1995; Norn, 1973), was introduced in the Phase 3 studies. Decreases in lissamine green staining indicate improved conjunctival health.

3.1.1.2 Schirmer Tear Test

The Schirmer tear test is a standard way to measure aqueous production. The test without anesthesia measures both normal aqueous secretion and stimulated aqueous secretion; the test with anesthesia blocks stimulated secretion and measures only the normal flow (also referred to as basal secretion). Lemp and Chacko (1997) have noted that the Schirmer test has been criticized for its lack of reproducibility because the degree of stimulation associated with the test is quite variable, but that the test is useful when the results are consistent over several visits. Wetting of less than 5 mm of the Schirmer strip after 5 minutes (less than 3 mm when anesthesia is used) is considered suggestive of an aqueous tear deficiency (Lemp and Chacko, 1997). Increases in Schirmer values in mm/5 minutes are considered indicative of improved aqueous production.

3.1.2 SUBJECTIVE MEASURES

Subjective measures assess the symptomatic component of the disease as reported by the patient.

3.1.2.1 Symptom Questionnaire

Patient symptoms that are frequently evaluated, using a variety of grading scales, include blurred vision, burning/stinging, dryness, itching, pain, sandy or gritty feeling, and sensitivity to light. Decreased scores indicate a reduction in the intensity of the specific symptom evaluated.

3.1.2.2 Composite Symptom Score

A composite symptom score was constructed by the Sponsor to more closely reflect the patient's discomfort profile by summing across 7 individual symptoms: blurred vision, burning and stinging, pain, itching, dryness, sensitivity to light, and sandy/gritty feeling. Decreases in the composite symptom score indicate a decrease in ocular discomfort (improvement).

3.1.2.3 Artificial Tear Use

Because of the severity of KCS in the patient population studied and the expectation that topical cyclosporine might not work immediately, patients had access to artificial tears as needed during the study. A decrease in the use of artificial tears (REFRESH®) over the course of the study was used as a measure that patients were benefiting from their study treatment and were relying less on artificial tears to relieve their dry-eye symptoms.

3.1.2.4 Ocular Surface Disease Index©

The OSDI© is a recently-developed, validated questionnaire designed by the Sponsor to provide a rapid assessment of the symptoms of KCS consistent with dry-eye disease and their impact on vision-related functioning. This questionnaire was used in the Phase 2 study and was concurrently and independently validated in a well-controlled clinical study after initiation of Phase 3 enrollment (OSDI© Validation Final Report). The validation study included 109 patients with KCS and 30 normal controls enrolled at a single study center. The study indicated that the OSDI© is more sensitive in assessing disease severity in patients with severe dry eyes than in those with mild or moderate disease. Decreases in the OSDI© score indicate a decrease in ocular discomfort and improvement in vision-related function.

3.1.2.5 Facial Expression Subjective Rating Scale

Facial expression illustrations have been used in chronic pain studies to evaluate subjective symptoms. The facial expression instrument used in these studies consisted of 9 expressive

faces, ranging from the happiest to the unhappiest face, categorized into 5 grades. It has previously been used in dry-eye studies in Japan (Tsubota, 1992). Decreases in the facial expression subjective rating scale indicate a decrease in ocular discomfort (improvement).

3.1.3 SPECIALIZED LABORATORY TESTS

Specialized laboratory tests refer to nonstandard, complex specialized tests performed in a research setting on a smaller subset of patients.

3.2 DESIGNING THE PHASE 3 CLINICAL EFFICACY AND SAFETY PROGRAM

When the Sponsor began designing clinical studies for a new topical ophthalmic preparation of cyclosporine, it had a solid base of clinical pharmacology data from the systemic drug literature. Prior to the initiation of the Sponsor's cyclosporine-KCS program, 3 multicenter clinical studies using an ointment preparation for the treatment of dry-eye disease had been conducted by Sandoz. Additionally, extensive use of topical ophthalmic cyclosporine for a broad variety of human ocular conditions had been reported in the literature (Foulks et al, 1996 [study report K206]; Gündüz and Özdemir, 1994; Helms et al, 1996 [study report K203]; Hingorani et al, 1999; Laibovitz et al, 1993; Power et al, 1993). Furthermore, topical ophthalmic cyclosporine had been studied in the treatment of chronic, idiopathic KCS in the dry-eye dog (Kaswan et al, 1989; Kaswan and Salisbury, 1990; Morgan and Abrams, 1991; Olivero et al, 1991). Cyclosporine ointment 0.2% (OPTIMMUNE®) was approved for the treatment of KCS in veterinary use in 1995. Using these studies and the tests described in the previous section, the Sponsor created the clinical program summarized in the following section.

3.2.1 DOSAGE AND REGIMEN

To establish the dosage to be used in the Sponsor's clinical program, doses used in previous studies with topical cyclosporine were evaluated.

Based on the information from all of these sources, doses ranging from 0.05% to 0.4% were chosen for the Sponsor's Phase 2 clinical trial.

The twice-daily regimen was selected based on ocular pharmacokinetic studies.

3.2.2 PATIENT SELECTION CRITERIA

In order to select a population of patients with moderate to severe KCS with or without Sjögren's syndrome, patients were required to exhibit predefined objective KCS findings and subjective symptoms. Exclusion criteria included patients using medications, devices, or undergoing procedures known to affect a dry-eye condition; and patients whose dry-eye disease was secondary to a primary disease condition other than Sjögren's syndrome. These exclusions were not made because of safety concerns, but because it was thought that such conditions might confound interpretation of study results.

Based on additional inclusion criteria, eligible patients with moderate to severe KCS included those who:

- had Schirmer values (without anesthesia)
- additionally, in the same eye, had a score of or more for the sum of corneal and interpalpebral conjunctival staining (with a corneal staining score of and

- met predefined criteria on the Ocular Surface Disease Index© (OSDI©) questionnaire and the facial expression subjective rating scale.

Patients were excluded:

- with nasal-stimulated Schirmer readings
-
- if they had a history of

A retrospective diagnosis of Sjögren's syndrome was

3.2.3 DURATION OF STUDIES

Building on the results of the Phase 2 study that included 12 weeks of treatment with study medication (study report 192371-001), treatment duration was extended in the Phase 3 studies to evaluate efficacy at the end of a 6-month Vehicle-Controlled Masked Treatment Phase. Several specialized laboratory tests were included in the Phase 3 studies to directly evaluate measures of the underlying pathophysiology of dry-eye disease, the target of cyclosporine therapy. A 6-month treatment period allowed sufficient time to observe these endpoints. In addition, the Phase 3 studies have a 6-month Cyclosporine Treatment Extension Phase in which patients who received 0.05% or 0.1% cyclosporine ophthalmic emulsion continue on the same masked regimen, while vehicle-treated patients are switched to 0.1% cyclosporine ophthalmic emulsion. The decision to switch vehicle patients to the higher cyclosporine concentration was made prospectively

3.2.8.2 Safety Testing

In addition to adverse event reporting, several routine ophthalmic safety tests were conducted, including visual acuity measurements, measurement of intraocular pressure (IOP), and biomicroscopy. Additionally, in the Phase 2 study (192371-001), blood chemistry and hematology were evaluated for all patients.

The effects of topical cyclosporine administration on ocular microflora were evaluated by analyzing adverse event reports of ocular infections in the clinical trials and by determining any qualitative and semi-quantitative changes in ocular microflora in a subset of patients in the Phase 2 study who were sampled using

No changes from baseline were observed in any blood chemistry and hematology endpoints, no increases were observed in ocular flora in the cyclosporine groups, and no ocular infections occurred during the Phase 2 study.

3.3 PATIENT POPULATION

The Phase 3 studies 192371-002 and 192371-003 (hereafter referred to as 002 and 003; study reports 192371-002 and 192371-003) had an identical double-masked, randomized, multicenter, and parallel-group design except for the inclusion of pharmacokinetic evaluations in study 002.

This was followed by the 6-month Vehicle-Controlled Masked Treatment Phase, when patients instilled 1 drop of 0.05% cyclosporine ophthalmic emulsion, 0.1% cyclosporine ophthalmic emulsion, or vehicle in each eye, twice daily (BID).

'. The analysis presented is based on the 6-month Vehicle-Controlled Masked Treatment Phase.

Across the treatment groups in the Phase 3 studies, age ranged from 22 to 90 years with a mean age of 60 years. More women (82%, 715/877) than men (18%, 162/877) were enrolled and patients were predominantly Caucasian (84%, 740/877). Of the 877 patients enrolled in the Phase 3 studies, 77% (671/877) completed the 6-month Vehicle-Controlled Masked Treatment Phase.

A rigorous and identical set of inclusion/exclusion criteria were defined in each of the 2 protocols. The objective was that a homogenous group of patients with moderate to severe disease would be recruited. The Sponsor believes that only patients meeting the inclusion/exclusion criteria were enrolled.

4.0 CLINICAL EFFICACY—PHASE 3 STUDIES

This section presents the key efficacy results of the Phase 3 studies (individually and in a pooled analysis), a brief overview of results for various subgroups (including patients with Sjögren's syndrome), and the results of specialized laboratory tests showing the effects of cyclosporine emulsion on the mechanisms underlying dry-eye disease.

4.1 INTENT-TO-TREAT ANALYSIS OF EFFICACY RESULTS

In the ITT analysis, all randomized patients were analyzed. For all efficacy variables collected for both eyes, only the worse eye was analyzed, defined as the eye adhering to entrance criteria and having the worse Schirmer without anesthesia and sum of corneal and interpalpebral conjunctival staining at baseline (Appendix 3 for description). If there was no visit within the per-protocol visit window (predefined intervals from baseline for each visit), then the last available observation was carried forward (LOCF) and used in the analysis.

Because of its ability to characterize the dry-eye population in these studies, an overall disease severity score replaced these original primary efficacy variables. Using factor analysis, an overall disease severity score was calculated to objectively define a single overall score that adequately reflected the overall severity of the disease

3.2.8. SAFETY ENDPOINTS

3.2.8.1 Pharmacokinetics

To determine the amount of cyclosporine absorbed into blood after topical ocular administration, pharmacokinetic parameters were evaluated in the Phase 2 study and one of the Phase 3 studies (192371-002). In the Phase 2 study, blood samples were taken after and weeks of treatment. Trough and peak (C_{max}) blood cyclosporin A (cyclosporine) concentrations were assessed. In the Phase 3 study, blood cyclosporin A trough concentrations were measured

Day 0 data (ie, baseline data prior to study medication) were not carried forward. All month 6 data were used, even if the visit occurred outside the visit window.

For each efficacy parameter, differences among the 3 treatment groups (referred to here as "among-group differences") were analyzed statistically to determine if there was a treatment effect. Where the among-group difference was statistically significant ($P \leq 0.05$), results of pairwise comparisons (which test 2 of the treatment groups at a time) are reported to provide further information.

In addition, for each individual treatment group, the change from baseline to each follow-up visit was analyzed ("within-group differences"). For the parameters discussed in the text, statistically significant ($P \leq 0.05$) among-group and within-group differences are identified. Footnotes to the tables included in the text identify the specific statistical tests used.

4.1.1 FACTOR (RESPONDER) ANALYSIS

In each study at month 6, significantly more patients responded to treatment with cyclosporine ophthalmic emulsion (43% to 50%) than to treatment with vehicle (29% to 31%).

4.1.2 OBJECTIVE EFFICACY MEASURES

Results for the individual components of the overall disease severity score are presented graphically in Figures 3 through 12 and in tabular form below.

4.1.2.1 Corneal Staining

In the Phase 3 studies, ocular staining was evaluated using the Oxford 6-point severity scale, which uses diagrams illustrating increasing severity (grades 0 to 5) to assist in standardizing grading by investigators (Appendix 4). Staining was analyzed as change from baseline for the worse eye, with a negative change indicating improvement.

Corneal staining is summarized for each of the Phase 3 studies in Section 9, Figures 5 and 6 and Table 4.1.2.1.

Table 4.1.2.1 Corneal Fluorescein Staining in Phase 3 Studies (Intent-to-Treat Population)

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=135[a]	CsA 0.1% N=134[a]	Vehicle N=136[a]	P value[b]	CsA 0.05% N=158[a]	CsA 0.1% N=158[a]	Vehicle N=156[a]	P value[b]
Day 0	2.84 ± 0.74	2.73 ± 0.82	2.72 ± 0.74	0.732	2.72 ± 0.85	2.70 ± 0.82	2.52 ± 0.73	0.036[d]
Change from baseline[c]:								
Month 6	–0.94 ± 1.01	–0.73 ± 1.08	–0.51 ± 1.03	0.008[e]	–0.84 ± 0.97	–0.93 ± 1.00	–0.78 ± 1.02	0.394

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Based on a 6-point severity scale (grades 0 to 5) using the worse eye. A negative change indicates improvement.

a The number of patients at day 0; sample sizes decreased at subsequent visits.

b Among-group P values from 2-way analysis of variance, with main effects of group and investigator.

c Within-group P values (from paired t-test) for change from baseline were significant ($P < 0.001$) for all treatment groups at all visits in both studies.

d Pairwise comparisons (from analysis of variance) showed higher baseline for 0.05% and 0.1% CsA vs vehicle ($P < 0.03$).

e Pairwise comparisons (from analysis of variance) favored 0.05% CsA vs vehicle ($P < 0.002$).

In study 002, improvement at month 6 was greatest with 0.05% cyclosporine emulsion, and the among-group difference was statistically significant, favoring 0.05% cyclosporine emulsion vs vehicle ($P = 0.002$).

In study 003, improvement was greatest with 0.1% cyclosporine emulsion at month 6. The vehicle group had significantly lower corneal staining at baseline.

4.1.2.2 Schirmer Tear Test with Anesthesia

The Schirmer tear test with anesthesia blocks stimulated secretion and measures only the normal flow (basal secretion). The Food and Drug Administration (FDA) requested that Schirmer values be evaluated by category. Accordingly, the Sponsor categorized Schirmer values from _____ for analysis (Appendix 4). A positive change from baseline indicates improvement. Results of the Schirmer tear test with anesthesia are summarized for each of the Phase 3 studies in Section 9, Figures 7 and 8 and Table 4.1.2.2.

Table 4.1.2.2 Categorized Schirmer Values With Anesthesia in Phase 3 Studies (Intent-to-Treat Population)

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=135[a]	CsA 0.1% N=133[a]	Vehicle N=136[a]	P value[b]	CsA 0.05% N=155[a]	CsA 0.1% N=154[a]	Vehicle N=152[a]	P value[b]
Day 0	2.10 ± 0.94	2.26 ± 1.06	2.23 ± 1.07	0.463	1.81 ± 0.95	1.90 ± 0.87	2.00 ± 1.03	0.221
Change from baseline:								
Month 6	0.41 ± 1.42[c]	0.21 ± 1.36	0.02 ± 1.43	0.066	0.36 ± 1.42[c]	0.31 ± 1.26[c]	-0.18 ± 1.06[c]	<0.001[d]

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Schirmer values categorized as [illegible] using the worse eye. A positive change indicates improvement.

a The number of patients at day 0; sample sizes decreased at subsequent visits.

b Among-group P values from Cochran-Mantel-Haenszel test.

c Significant within-group P values (from Wilcoxon's signed-rank test) for change from baseline ($P \leq 0.048$).

d Pairwise comparisons (from Cochran-Mantel-Haenszel test) favored 0.05% and 0.1% CsA vs vehicle ($P < 0.001$).

In study 002 at month 6, there was statistically significant improvement from baseline with 0.05% cyclosporine emulsion. The among-group difference approached statistical significance at month 6 ($P = 0.066$) with the greatest improvement shown in the 0.05% group in contrast to almost no change with vehicle.

In study 003 at month 6, there were statistically significant within-group improvements with both concentrations of cyclosporine emulsion in contrast to a significant worsening with vehicle; the among-group difference was statistically significant in favor of cyclosporine emulsion over vehicle ($P < 0.001$).

In both studies, improvement at month 6 was greatest with 0.05% cyclosporine emulsion.

4.1.3 SUBJECTIVE EFFICACY MEASURES

4.1.3.1 Blurred Vision

Results for blurred vision are summarized for each of the Phase 3 studies in Section 9, Figures 9 and 10 and Table 4.1.3.1. A decrease in the rating indicates improvement.

Table 4.1.3.1 Blurred Vision in Phase 3 Studies (Intent-to-Treat Population)

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=135[a]	CsA 0.1% N=134[a]	Vehicle N=136[a]	P value[b]	CsA 0.05% N=158[a]	CsA 0.1% N=158[a]	Vehicle N=156[a]	P value[b]
Day 0	2.22 ± 1.30	1.95 ± 1.27	1.85 ± 1.22	0.045[d]	1.89 ± 1.32	1.85 ± 1.28	1.81 ± 1.35	0.852
Change from baseline:								
Month 6	–0.55 ± 1.37[c]	–0.39 ± 1.18[c]	–0.22 ± 1.08[c]	0.127	–0.41 ± 1.19[c]	–0.38 ± 1.27[c]	–0.08 ± 1.46	0.263

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Graded on a scale from 0 (do not have symptom) to 4 (always notice symptom). A negative change indicates improvement.

a The number of patients at day 0; sample sizes decreased at subsequent visits.

b Among-group P values from Cochran-Mantel-Haenszel test.

c Significant within-group P values (from Wilcoxon's signed-rank test) for change from baseline ($P \leq 0.012$).

d Pairwise comparisons (from Cochran-Mantel-Haenszel test) showed higher baseline for 0.05% CsA vs vehicle ($P < 0.014$).

In study 002, there were statistically significant within-group improvements from baseline in blurred vision with 0.05% cyclosporine emulsion at month 6. Improvement was greater with either concentration of cyclosporine emulsion than with vehicle at month 6, although the among-group difference was not statistically significant.

In study 003, statistically significant within-group improvement from baseline was seen with both concentrations of cyclosporine emulsion at month 6.

4.1.3.2 REFRESH® Use

REFRESH® use is considered a subjective variable because it was based on patients' perception of their need for artificial tears. Mean daily REFRESH® use during the previous week is summarized for each of the Phase 3 studies in Section 9, Figures 11 and 12 and Table 4.1.3.2. A decrease in REFRESH® use indicates improvement.

Table 4.1.3.2 Daily REFRESH® Use During the Previous Week in Phase 3 Studies (Intent-to-Treat Population)

	Study 192371-002				Study 192371-003			
	CsA 0.05% N=133[a]	CsA 0.1% N=134[a]	Vehicle N=136[a]	P value[b]	CsA 0.05% N=157[a]	CsA 0.1% N=157[a]	Vehicle N=152[a]	P value[b]
Day 0	5.74 ± 8.33	5.03 ± 3.60	4.54 ± 2.76	0.315	6.69 ± 6.69	6.02 ± 4.63	5.14 ± 3.96	0.019[d]
Change from baseline:								
Month 6	−1.79 ± 7.12[c]	−1.23 ± 5.48[c]	−0.07 ± 5.87	0.124	−2.34 ± 6.05[c]	−1.51 ± 4.63[c]	−1.15 ± 6.64[c]	0.087

Note: CsA = cyclosporine ophthalmic emulsion. Values shown are mean ± standard deviation. Based on patient recorded times per day that REFRESH® was used during the previous week. A negative change indicates improvement.

a Number of patients at day 0; sample sizes decreased at subsequent visits.

b Among-group P values from 2-way analysis of variance, with main effects of group and investigator.

c Significant within-group P values (from paired t-test) for change from baseline ($P \leq 0.040$).

d Pairwise comparisons (by analysis of variance) showed higher baseline value for 0.05% CsA vs vehicle.

In study 002, the decrease in REFRESH® use was greater with either concentration of cyclosporine emulsion than with vehicle at month 6 (greatest with 0.05%).

In study 003, the decrease in REFRESH® use at month 6 was greater with either concentration of cyclosporine emulsion than with vehicle.

4.2 DIFFERENCES BETWEEN THE PHASE 3 STUDIES

In each of the Phase 3 studies, improvement from baseline was generally seen with each concentration of cyclosporine emulsion at each follow-up visit. However, several important differences are apparent in the ITT efficacy results between study 002 and study 003 when using individual variables or endpoints. Although the magnitude of improvement from baseline was at times greater in study 003 than in study 002 for both the 0.05% and 0.1% cyclosporine emulsion groups, statistically significant differences favoring cyclosporine over

vehicle were more frequently demonstrated in study 002 than study 003. This was due to the relatively strong vehicle response in study 003, which was evident as early as month 1 and persisted throughout the treatment period.

Baseline entry data indicate that the dry-eye populations enrolled in the 2 studies were not identical when relying on a single endpoint. For example, study 003 had a greater proportion of less severe dry-eye patients than study 002, as seen in the corneal staining scores. The mildest corneal staining score allowed at study entry was grade 2, which occurred in 53% of patients in study 003 compared with 42% of patients in study 002. Thus, the difference between the studies in patients with the lowest allowed grade of corneal staining was approximately 10 percentage points. This difference was further emphasized in the vehicle group, where 61% of the patients entered with grade 2 staining in study 003 and 41% of the patients entered with grade 2 in study 002, a difference of 20 percentage points. A similar but less pronounced pattern of milder baseline disease severity in study 003 compared with study 002 was seen for blurred vision and artificial tear use.

Although baseline data for multiple endpoints showed milder disease in study 003 than in study 002, this was not true for every variable. Baseline Schirmer scores tended to be lower (worse) in study 003 than in study 002. This is consistent with the frequently reported observation that signs and symptoms of dry-eye disease often do not correlate, and further underscores the complexity of dry-eye disease. This complexity substantiates the clinical relevance of selecting a representative group of variables to assess treatment response, since there is not a single endpoint that characterizes the disease. The importance of the responder analysis is thus underscored. The responder analysis at month 6 found that 43% (study 003) to 50% (study 002) of cyclosporine patients were classified as responders compared with 29% (study 003) to 31% (study 002) of vehicle patients in each of the Phase 3 studies. The responder rate with vehicle was not surprising because, as described earlier, the vehicle was expected to have beneficial effects.

4.3 POOLED ANALYSIS

A pooled analysis of the ITT population in studies 002 and 003 was performed to confirm that statistically and clinically relevant improvement in the individual endpoints for the signs

and symptoms of KCS would be apparent in the overall enrolled patient population. The pooled analysis was performed by combining all ITT data from both Phase 3 studies, and pooling investigators by geographic region within each of the Phase 3 studies.

Breslow-Day's test for 2x2 tables was used to test for homogeneity between studies (002 and 003) in paired comparisons of responder rates (Breslow and Day, 1980). For all 3 pairwise comparisons of responder rates, there were no statistically significant differences between studies. Therefore, homogeneity is not of concern in pooling the data from these 2 studies.

The statistically significant among-group differences in the pooled analysis are summarized in Table 4.3.

Table 4.3 Statistically Significant Among-Group Differences in the Pooled Analysis of Phase 3 Studies (Intent-to-Treat Population)

Parameter	Statistically Significant Among-Group Differences[a]	Statistically Significant Pairwise Comparisons Favored:
Corneal staining	Month 6 (P = 0.023)	0.05% CsA vs vehicle
Categorized Schirmer with anesthesia	Month 6 (P < 0.001)	0.05% and 0.1% CsA vs vehicle
Blurred vision	Month 6 (P = 0.044)	0.05% CsA vs vehicle
REFRESH® use	Month 6 (P = 0.013)	0.05% CsA vs vehicle
Treatment success[b]	Month 6 (P = 0.041)	0.05% CsA vs 0.1% CsA and vehicle

Note: CsA = cyclosporine ophthalmic emulsion.
a Among-group P values from analysis of variance (for staining and REFRESH® use) and Cochran-Mantel-Haenszel test (for Schirmer test, symptoms, and global response), and Fisher's exact test (for treatment success).
b The number of patients who had a global response of almost cleared or completely cleared.

The pooled analysis found statistically significant among-group differences in favor of 0.05% cyclosporine emulsion in the key efficacy parameters of corneal staining, categorized Schirmer with anesthesia, blurred vision, and REFRESH® use. Thus, the pooled analysis confirmed that the statistically and clinically relevant improvement from baseline in signs and symptoms seen in the individual studies was apparent in the Phase 3 patient population overall.

4.4 SUBGROUP ANALYSES

4.4.1 SJÖGREN'S SYNDROME SUBGROUP

A subgroup analysis evaluated efficacy in patients with Sjögren's syndrome. Based on criteria defined by Vitali et al (1993) and provided in Appendix 3, the number of Sjögren's patients identified for this subgroup analysis may underestimate the number in the study population because some patients left the studies without having autoantibody data collected, and therefore could not meet the study criteria for Sjögren's syndrome.

This subgroup included 31% (270/877) of patients across both Phase 3 studies. A greater proportion of the patients were female in the subgroup of patients with Sjögren's syndrome than in the ITT population, 92% (247/270) compared to 82% (715/877).

Results in patients with Sjögren's syndrome were similar to those in the ITT population in that improvement from baseline was generally seen within each treatment group, with several of the among-group differences reaching statistical significance in study 002.

4.4.2 OTHER SUBGROUPS ANALYZED

Subgroup analyses also were performed in patients with severe disease, in the per-protocol subgroup, by age category, by race category, by sex, and by iris color. Results from these analyses established that the efficacy of cyclosporine emulsion is not limited to a specific subgroup. Compared with the intent-to-treat analyses, there were no notable new findings in either study 002 or study 003 in these subgroup analyses.

4.5 SPECIALIZED LABORATORY TESTS

Procedures for all specialized laboratory tests were conducted in the worse eye as identified by the investigator at the qualification examination based upon results of the Schirmer test without anesthesia and sum of corneal and interpalpebral conjunctival staining.

5.0 SAFETY

5.1 OVERVIEW

The safety of cyclosporine (cyclosporin A) is well defined by more than 2 decades of study in animals and in humans. In addition to the thousands of patients who rely daily on cyclosporine, many research studies have used cyclosporine as an investigational probe. Allergan has developed an ophthalmic emulsion formulation of cyclosporine that, when used topically, is well tolerated and does not result in meaningful systemic exposure. Blood concentrations following ocular instillation of cyclosporine ophthalmic emulsion are nearly undetectable in humans and are thousands of times lower than blood concentrations measured during oral cyclosporine treatment of rheumatoid arthritis and psoriasis patients.

This minimal systemic exposure correlates with the lack of systemic toxicity seen during ophthalmic treatment.

Clinical studies demonstrated that cyclosporine ophthalmic emulsion was well tolerated locally, with ocular adverse events that were not unexpected given patients with an ophthalmic disease and the topical study medication. The most common ocular adverse events were burning, stinging, visual disturbance, conjunctival hyperemia, eye pain, discharge, pruritus, foreign body sensation, photophobia, and irritation. There were no clinically significant changes in visual acuity, intraocular pressure, or biomicroscopy. Systemic adverse events were generally similar in treated and control patients.

In clinical studies, no ocular infections were reported for patients receiving cyclosporine ophthalmic emulsion for up to 6 months. Ocular microbial analyses of conjunctival bacterial isolates indicated that treatment with cyclosporine ophthalmic emulsion was associated with a decrease from baseline in abnormal organisms. Thus overall, there was no sign of local immunosuppression during treatment with cyclosporine ophthalmic emulsion.

Cyclosporine 0.05% emulsion is considered safe for therapeutic use in patients with dry-eye disease.

5.2 ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION

5.2.1 SYSTEMIC ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION IN ANIMALS AND HUMANS

Systemic blood concentrations following ophthalmic instillation of cyclosporine emulsion in humans are nearly undetectable, and are thousands of times lower than blood concentrations measured during oral cyclosporine treatment of rheumatoid arthritis and psoriasis patients. The low systemic exposure is due to the low dose instilled, extensive metabolism of cyclosporine in the liver, and a moderately short half-life in blood. These factors prevent extensive systemic accumulation. This low degree of systemic exposure is reflected in the lack of drug-related, systemic adverse events reported during toxicological studies in animals and clinical studies in humans.

In the clinical Phase 2 study and Phase 3 study 002, blood samples were assayed using a validated

method with a lower limit of quantitation of 0.1 ng/mL. In the 12-week Phase 2 study of 0.05% to 0.4% cyclosporine emulsion BID in both eyes, mean blood cyclosporin A concentrations were below the quantitation limit in all 0.05% and 0.1% cyclosporine emulsion-treated patients at all sampling times. The highest individual blood concentration measured in any patient taking 0.05% or 0.1% cyclosporine emulsion was 0.102 ng/mL. The highest blood concentration measured in any individual patient in any treatment group was 0.158 ng/mL in a patient treated with 0.4% cyclosporine emulsion.

In Phase 3 study 002 of 0.05% and 0.1% cyclosporine emulsions BID in both eyes, mean blood cyclosporin A concentrations were below the quantitation limit in both treatment groups at all sampling times. Out of 224 trough blood samples collected from patients treated with cyclosporine emulsion, and 208 serial blood samples collected from 26 cyclosporine emulsion-treated patients over 1 dosing interval, only 10 samples contained quantifiable cyclosporin A. All 10 of these samples were from 0.1% cyclosporine emulsion-treated patients, and the highest of them contained 0.299 ng/mL. All of the other 422 samples, including all samples from patients treated with 0.05% cyclosporine emulsion, were below the quantitation limit of 0.1 ng/mL.

The NEORAL® (Novartis tradename for an oral formulation of cyclosporine) labeling indicates that treatment of rheumatoid arthritis and psoriasis patients with oral cyclosporine produced blood concentrations (mean ± standard deviation) that ranged from a trough of 74.9 ± 46.7 ng/mL to a C_{max} of 655 ± 186 ng/mL to 728 ± 263 ng/mL (PDR - NEORAL®, 1998). Blood concentrations produced by topical application of cyclosporine ophthalmic emulsion are at least several orders of magnitude below those produced by systemic cyclosporine treatments already approved for non-life-threatening conditions (Table 5.2.1). These low blood concentrations support the absence of any observed systemic effect during Phase 3 clinical studies.

Table 5.2.1 Comparison of Dose and Subsequent Mean Blood C_{max}, $C_{average}$, C_{min}, and AUC_{0-12} Between Systemic Therapeutic Use of NEORAL® and Topical Use of 0.05% Cyclosporine Emulsion

Parameter	NEORAL®[a]	0.05% Cyclosporine Ophthalmic Emulsion[b]	Ratio NEORAL®/Cyclosporine Ophthalmic Emulsion
Dose[c] (mg/day)	189	0.0570	3320
C_{max} (ng/mL)[c]	655	< 0.1	> 6550
$C_{average}$ (ng/mL)[d]	194	< 0.1	> 1940
C_{min} (ng/mL)[e]	74.9	< 0.1	> 749
AUC_{0-12} (ng•hr/mL)[c]	2324	< 1.2	> 1940

a Blood cyclosporine concentrations during oral NEORAL® treatment of rheumatoid arthritis or psoriasis.
b Blood cyclosporin A concentrations during ophthalmic treatment with cyclosporine emulsion.
c PDR - NEORAL®, 1998 (for NEORAL®) and study report PK-98-112 (for cyclosporine emulsion).
d Calculated as AUC_{0-12} (ng·hr/mL) / 12 hours.
e PDR - NEORAL®, 1998 (for NEORAL®) and study report PK-98-109 (for cyclosporine emulsion).

5.2.2 OCULAR ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION IN ANIMALS

Cyclosporine is a lipophilic molecule that is soluble in oil but nearly insoluble in water. Its ____ $^{oil}/_{water}$ partition coefficient is more than 10,000, so virtually all of the cyclosporine in a _____. emulsion is dissolved in the oil droplets.

Table 5.2.2 Pharmacokinetic Parameters in Selected Ocular Tissues after BID Ophthalmic Administration of 0.05% to 0.2% Cyclosporine Emulsion to Rabbits and Dogs for 7 to 9 ½ Days

5.2.3 OCULAR ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION IN HUMANS

Cyclosporine concentrations in human ocular tissues were not measured during treatment with the Sponsor's ophthalmic emulsion, but have been measured during ophthalmic treatment with other cyclosporine formulations (Minguez et al, 1992; Perry et al, 1998). Human corneal concentrations during ophthalmic BID treatment with 0.05% cyclosporine

emulsion have been predicted from the work of Perry et al and from results of ocular distribution studies in rabbits (study report PK-98-074) and dogs (study report PK-96-016) treated with cyclosporine ophthalmic emulsion BID.

Perry et al, using a different formulation, have reported that human corneal concentrations are approximately 3,700 ng/g after ocular instillation of a 0.5% aqueous solution of cyclosporine every 15 minutes for 1 hour

These derivations produce consistent estimates of human corneal C_{max}, and suggest that corneal C_{max} in humans is 450 to 620 ng/g. This range compares favorably to the mean cyclosporine concentration of 236 ng/g measured in human corneas after topical instillation of 5 to 10 eyedrops of 2% cyclosporine solution in olive oil beginning 1 day before kerotoplasty surgery (Minguez et al, 1992).

Ocular metabolism was not investigated in humans because fresh human ocular tissues were unavailable for incubation. Due to the time required for the preparation and transportation of human eyes, ocular tissue is usually received at least 24 to 36 hours after death, at which time the activities of ocular metabolic enzymes may be substantially reduced from their in vivo levels. Constitutive cytochrome P-450 activities in rabbit, dog, and human ocular tissues are very low, but are qualitatively similar. Based on the complete absence of metabolism in rabbit ocular tissues, it is likely that metabolism in human ocular tissues is minimal if it occurs at all. Although there are no data to confirm the lack of ocular metabolism in humans, this information is not fundamental to assessing the ocular safety of cyclosporine given the lack of metabolism in rabbit and dog eyes, the low cytochrome P-450 activities in rabbit and human eyes, and the demonstrated safety of cyclosporine emulsion treatment in rabbits and humans for up to 6 months and in dogs for up to 1 year.

5.3 SYSTEMIC SAFETY

5.3.1 SYSTEMIC FINDINGS IN NONCLINICAL STUDIES

Extensive single and repeat-dose systemic toxicological studies that were conducted by Sandoz (now Novartis Pharmaceutical Corporation) in a number of animal species established the safety of cyclosporine for human therapeutic use administered orally or parenterally (PDR-NEORAL®, 1998). Safety studies conducted by Schering-Plough in the development of topical cyclosporine for veterinary use (OPTIMMUNE®) also indicated excellent local tolerance and an absence of cyclosporine-related systemic side effects (NADA 141-052, 1995). Additional clinical evidence supporting the long-term safety and efficacy of topical cyclosporine is provided by veterinary ophthalmologists, who have applied topical cyclosporine since 1989 for treatment of ocular surface inflammatory disease and idiopathic KCS in the dog, cat and horse (Williams DL, 1997; Sansom J et al, 1995).

The Sponsor conducted a number of toxicological studies in support of the safety of

Based on the toxicological studies in rabbits and dogs, there is an excellent margin of safety for the therapeutic use of 0.05% cyclosporine ophthalmic emulsion BID in humans with dry-eye disease.

5.3.2 SYSTEMIC ADVERSE EVENTS IN PHASE 3 CLINICAL TRIALS

The nonclinical safety data were reinforced by clinical data from the Phase 3 studies 002 and 003. Because these studies had the same design, their safety data were pooled. The

information reported here is from the 6-month Vehicle-Controlled Masked Treatment Phase. The 6-month duration was agreed to with the FDA prior to study initiation as being an adequate amount of time to evaluate the clinical safety given the topical ophthalmic route of administration, the proposed indication for KCS, and the experience with cyclosporine as an approved systemic drug. _____

_____

_____

One or more adverse events were reported for 56.7% (166/293) of patients treated with 0.05% cyclosporine emulsion, 63.0% (184/292) of those treated with 0.1% cyclosporine emulsion, and 57.9% (169/292) of those treated with vehicle. The types of adverse events and incidences were generally similar among the 3 treatment groups, and were consistent with what would be expected with an older population studied for 6 months. Adverse events which led to discontinuation of the study medication are summarized by body system in Appendix 5, Table 1. Systemic adverse events reported by at least 3% of patients (9 patients) in either of the cyclosporine emulsion groups are listed by body system in Table 5.3.2.

Table 5.3.2 **Number (%) of Patients in the Phase 3 Studies with Systemic Adverse Events Reported by ≥ 3% of Patients in Either Cyclosporine Group**

COSTART Body System/ Preferred Term	0.05% Cyclosporine N=293	0.1% Cyclosporine N=292	Vehicle N=292
Body as a Whole			
Infection	18 (6.1)	23 (7.9)	29 (9.9)
Flu syndrome	13 (4.4)	6 (2.1)	13 (4.5)
Headache	11 (3.8)	11 (3.8)	7 (2.4)
Cardiovascular			
Hypertension	10 (3.4)	4 (1.4)	7 (2.4)
Respiratory			
Infection sinus	9 (3.1)	7 (2.4)	13 (4.5)

Systemic infections (primarily colds and upper respiratory infections), flu syndrome, headache, hypertension, and sinus infection were reported at similar or higher rates in the

vehicle group than in the cyclosporine emulsion groups. In all treatment groups, isolated abnormal laboratory test results were reported as adverse events; however, none was thought by the investigator or the medical monitor to be related to the study medication.

Nephrotoxicity and hepatotoxicity were not seen in these studies.

In the Phase 3 studies, serious adverse events (SAEs) were reported for 5.8% (17/293) of patients in the 0.05% cyclosporine emulsion group, 6.8% (20/292) of those in the 0.1% cyclosporine emulsion group, and 4.8% (14/292) of those in the vehicle group. Each SAE was considered by the investigator to have either no relationship to study medication or unlikely to be related to study medication.

Among the SAEs, there were 5 deaths during the Phase 3 studies.

As with the other SAEs, each death was considered by the investigator to have either no relationship to study medication or unlikely to be related to study medication.

In addition, 2 patients experienced SAEs in the Phase 2 study, neither of which was considered to be related to treatment.

For the Phase 3 studies, adverse events were examined for the following subgroups: age (< 40 years, 40 to 64 years, and > 64 years), sex, race (Caucasian including Hispanic and non-Caucasian), diagnosis (Sjögren's syndrome and non-Sjögren's), and iris color (dark and light). Although some differences among some of the subgroups were noted, there were no apparent patterns by treatment group. Overall, adverse events were reported for a higher proportion of females (60.8%, 435/715) than males (51.9%, 84/162), and a higher proportion of patients with Sjögren's syndrome (66.7%, 180/270) than non-Sjögren's patients (55.8%, 339/607).

5.3.3 LABORATORY DATA

Blood chemistry and hematology were evaluated in the Phase 2 study at

The majority of patients in the cyclosporine emulsion and vehicle groups had normal values at all visits. Changes from baseline occurred in only small numbers of patients, were in both directions, and were considered by the medical monitor to be neither clinically significant nor related to study medication. Differences among the treatment groups were generally not statistically significant. No patients experienced laboratory adverse events related to blood chemistry or

hematology parameters. No important changes from baseline were observed in any blood chemistry and hematology endpoints, and no increases were observed in ocular flora in the cyclosporine groups during the Phase 2 study.

5.4 OCULAR SAFETY

5.4.1 OCULAR FINDINGS IN NONCLINICAL STUDIES

Thus, based upon the ocular and systemic safety of cyclosporine emulsion administered under exaggerated conditions for up to 1 year in animal studies, the proposed clinical use of 0.05% cyclosporine ophthalmic emulsion is considered safe for therapeutic use in humans.

5.4.2 OCULAR ADVERSE EVENTS IN PHASE 3 CLINICAL TRIALS

One or more adverse events in the special senses body system were reported for 34.8% (102/293) of patients treated with 0.05% cyclosporine emulsion, 42.1% (123/292) of those treated with 0.1% cyclosporine emulsion, and 30.5% (89/292) of those treated with vehicle. Ocular adverse events reported by at least 3% of patients (9 patients) in either of the cyclosporine emulsion groups are listed in Table 5.4.2.

Table 5.4.2 **Number (%) of Patients in the Phase 3 Studies with Ocular Adverse Events Reported by ≥ 3% of Patients in Either Cyclosporine Group**

COSTART Body System/ Preferred Term	0.05% Cyclosporine N=293	0.1% Cyclosporine N=292	Vehicle N=292
Special Senses			
Burning eye	47 (16.0)	51 (17.5)	21 (7.2)
Discharge eye	14 (4.8)	7 (2.4)	8 (2.7)
Foreign body sensation	11 (3.8)	7 (2.4)	8 (2.7)
Conjunctival hyperemia	11 (3.8)	12 (4.1)	2 (0.7)
Stinging eye	10 (3.4)	14 (4.8)	5 (1.7)
Irritation eye	9 ([illegible]	5 (1.7)	5 (1.7)
Visual disturbance	9 ([illegible]	15 (5.1)	18 (6.2)
Pruritus eye	8 (2.7)	13 (4.5)	10 (3.4)
Photophobia	7 (2.4)	9 (3.1)	3 (1.0)
Eye pain	5 (1.7)	17 (5.8)	8 (2.7)

Ocular burning was reported more frequently in the 0.05% and 0.1% cyclosporine emulsion groups (by 16.0% and 17.5% of patients, respectively) than in the vehicle group (7.2%). Conjunctival hyperemia and stinging eye showed a similar pattern but were reported by fewer patients overall than ocular burning. Other ocular adverse events showed no notable differences among the treatment groups. The majority of ocular events were mild to moderate in severity and, while considered to be related to the study medications, were not serious or enduring. Ocular adverse events that led to discontinuation of the study medication are listed by treatment group in Appendix 5, Table 2.

Those adverse events categorized as "visual disturbance" were most often described in terms of blurred vision. These were ocular in origin rather than the syndrome of central nervous system toxicity and cortical blindness reported with systemic cyclosporine use (Ghalie et al, 1990; Memon et al, 1995; Nussbaum et al, 1995).

Ocular infections were reported for 2 patients in the Phase 3 studies, both of whom were in the vehicle treatment group. There was no indication of harmful local immunosuppression during treatment with cyclosporine ophthalmic emulsion.

5.4.3 OTHER SAFETY ASSESSMENTS IN PHASE 3 CLINICAL TRIALS

Visual acuity, intraocular pressure, and slit-lamp biomicroscopy were adjunctive safety assessments in the Phase 3 studies. There were no clinically important safety findings for any of these variables.

5.4.4 OCULAR MICROBIOLOGY

In addition to tracking the occurrence of any ocular infections that occurred during the clinical studies, the Sponsor examined ocular flora in the Phase 2 study before and after 12 weeks of treatment with cyclosporine ophthalmic emulsion to see if there were any changes that might suggest an increased propensity to develop ocular infections. There is little published information on ocular flora in normal human eyes, and even less on ocular flora in clinically pathological conditions such as dry eye. However, *E. coli* and other ocular pathogens have been reported in the ocular flora of dry-eye dogs (Salisbury, 1995) and in dry-eye patients (Castillo et al, 1994).

The Phase 2 vehicle-controlled study (192371-001) evaluated the effects of concentrations of cyclosporine ophthalmic emulsion as high as 0.4%. Conjunctival microbiology was performed in 74 patients at 4 of the 9 study centers. _____

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_____. At the baseline visit, 48% (32/66) of patients were culture positive (8 patients were missing baseline data but had follow-up data); 53 bacterial strains comprising 22 species of microorganisms were identified.

Table 5.4.4-1 presents the most frequently cultured organisms in the patients treated with vehicle and the patients treated with cyclosporine emulsion, all concentrations combined.

Table 5.4.4-1 Number (%) of Patients in Phase 2 Study with Most Frequently Reported Organisms

No significant changes in the microbial ocular flora were observed following treatment with cyclosporine emulsion (Table 5.4.4-2).

Table 5.4.4-2 Number (%) of Patients in Phase 2 Study with Organisms Isolated

The number of culture-positive patients in the cyclosporine emulsion groups was approximately the same at each visit. In the cyclosporine emulsion groups there was a trend toward fewer bacterial species and fewer total strains of organisms at the end of treatment

(week 12) and posttreatment (week 16) compared to baseline. Conversely, in the vehicle group there was a trend toward an increased number of organisms at week 12, with a return to baseline levels posttreatment at week 16.

Although there were variations in the microbial flora over the course of the study, these were similar among the treatment groups. Changes in microbial flora from baseline to the end of treatment and posttreatment are summarized in Tables 5.4.4-3 and 5.4.4-4, respectively.

Table 5.4.4-3 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora after 12 Weeks of Treatment

Table 5.4.4-4 Number (%) of Patients in Phase 2 Study with Changes in Microbial Flora 4 Weeks Post-Treatment

There were no ocular infections or other clinical signs or symptoms thought to be due to microbial changes in the ocular flora of the cyclosporine emulsion groups during the Phase 2 study (including the treatment and posttreatment periods). There was one report of conjunctivitis of unknown etiology in the vehicle group. There did not appear to be an overgrowth of ocular microorganisms with any of the treatments.

As mentioned in Section 5.4.2, in the 2 well-controlled Phase 3 studies ocular infections were reported for 2 patients, both of whom were in the vehicle group. Thus, during treatment with cyclosporine ophthalmic emulsion in the Sponsor's clinical trials there was no indication of harmful local immunosuppression leading to changes in ocular flora or to clinical infection.

The results of the Phase 2 study are similar to results reported in dogs with KCS. The effect of topical administration of 2% cyclosporine eye drops (in oil) on the number and type of microorganisms isolated from the corneal surface of dogs with KCS has been studied by Salisbury et al (1995). Before treatment, 93% (57/61) of the eyes showed microbial growth. The most commonly isolated microbes were *Staphylococcus* and *Streptococcus* organisms. In eyes that responded to treatment (Schirmer tear test value increased by $\geq$ 5 mm/min compared with pretreatment value), the percentage of eyes from which bacteria were isolated after 3, 6, and 12 months of treatment was significantly less ($P < 0.001$) than the percentage from which bacteria were isolated at baseline (pretreatment). Among eyes that did not respond to treatment, a significant change over time in prevalence of bacteria or type of bacteria isolated was not found. Opportunistic corneal infections were not detected. The investigators suggest that an increase in production of tears, which contain anti-infective proteins, was the primary factor responsible for the decrease in the percentage of eyes from which microorganisms could be isolated. There was no evidence that cyclosporine caused opportunistic microbial overgrowth or that it had more than a minimal direct antimicrobial effect.

In KCS patients, Castillo et al (1994) quantitatively determined microorganisms before and after punctal occlusion and compared them with normal age-matched subjects. Dry-eye patients had increased numbers of colony-forming units (CFUs) as well as pathogenic organisms prior to punctal occlusion. A significant reduction of organisms isolated after punctal occlusion similar to that in normal controls suggests the need for adequate tears to maintain a normal ocular flora.

In conclusion, no ocular infections were reported in patients treated with cyclosporine ophthalmic emulsion. Although an increase in ocular flora would not necessarily be

clinically relevant and associated with ocular infection, both the reduction in the types of organisms cultured and the absence of ocular infections seen in the Sponsor's cyclosporine clinical studies show no tendency toward development of a compromised ocular environment in KCS patients treated with cyclosporine ophthalmic emulsion. In fact, cyclosporine emulsion may benefit KCS patients by improving the antibacterial environment through its beneficial effects on the underlying dry-eye condition.

5.5 SAFETY PROFILE FOR OTHER FORMULATIONS OF TOPICAL OPHTHALMIC CYCLOSPORINE

Safety data from studies using other formulations of topical ophthalmic cyclosporine may not be necessarily relevant to the current application. However, they are presented here as general support for the overall safety of topical ophthalmic cyclosporine.

Six studies not conducted by the Sponsor have reported on the use of non-emulsion formulations of topical ophthalmic cyclosporine in 364 patients with KCS (Foulks et al, 1996 [study report K206]; Gündüz and Özdemir, 1994; Helms et al, 1996 [study report K203]; Laibovitz et al, 1993; Power et al, 1993; study report K201). Five of these studies were placebo or vehicle-controlled. The studies used either a [redacted] (SANDIMMUNE®, Novartis tradename for an oral formulation of cyclosporine,) [redacted] with cyclosporine in concentrations from 0.5% to 2% and administered from 1 to 4 times daily for 2 to 8 weeks. In the largest study (Helms et al, 1996; 256 patients), the most frequent adverse events were burning and blurred vision. Twenty-five patients discontinued due to adverse events, most due to ocular burning. The only other notable safety finding among these studies was that 2 patients after developed an epitheliopathy that resolved after discontinuing treatment with 2% cyclosporine in [redacted]

Literature published since 1985 includes reports on the use of other formulations of topical ophthalmic cyclosporine in vernal keratoconjunctivitis, corneal transplants, corneal ulcers, herpetic stromal keratitis, necrotizing scleritis, multiple indications, and healthy volunteers (see "other indication" references). In these studies, topical cyclosporine was administered 1 to 5 times daily, in concentrations of 2% or less. In the studies where adverse events were noted, they were minimal and consisted of transient burning, punctate epitheliopathy or

keratitis. No serious adverse events were reported, and only 6 patients were discontinued due to adverse events (BenEzra et al, 1988; Holland et al, 1993; Secchi et al, 1990). No abnormal clinical laboratory findings were reported, except for transient, asymptomatic, and unexplained elevations of serum transaminases in 5 healthy volunteers (Solch et al, 1991).

Following topical administration, cyclosporine was not detected in blood or serum using _____ (limit of detection from 5 to 50 ng/mL) in 6 of these studies, and low levels of cyclosporine (≤ 64 ng/mL) were detected using _____ of these studies (see "other indication" references).

Two additional placebo-controlled trials were conducted of 2% SANDIMMUNE® ophthalmic ointment administered for 18 months to 443 high risk corneal transplant patients for the prevention of graft failure (study reports K204 and K301). Adverse events were mild or moderate in the majority of cases, and their incidence did not differ between the SANDIMMUNE® and placebo groups. Laboratory abnormalities during follow-up were similar in both treatment groups. Blood cyclosporine concentrations were undetectable, except for rare, non-reproducible values in a small number of patients.

5.6 DRUG-DRUG INTERACTIONS

No formal drug interaction studies with cyclosporine ophthalmic emulsion were conducted. In humans, systemic exposure from topical ophthalmic cyclosporine emulsion is minimal, and thus no significant interactions with systemic drugs are expected. There is no information regarding potential interactions of topical ophthalmic drugs coadministered with cyclosporine emulsion because such drugs were prohibited during the Phase 2 and Phase 3 studies.

5.7 DRUG ABUSE AND OVERDOSAGE

There is no experience with overdosage in humans using topical cyclosporine ophthalmic emulsion. Excessive topical use of cyclosporine ophthalmic emulsion would not be expected to contribute to any ocular toxicity. Due to low systemic concentrations of cyclosporine

after topical treatment with the ophthalmic emulsion, the likelihood of systemic intoxication from topical overdose is remote.

A single unit-dose vial of 0.05% cyclosporine ophthalmic emulsion contains 0.2 mg of cyclosporine. The recommended weight-normalized starting dose of systemically administered cyclosporine for rheumatoid arthritis and psoriasis is 2.5 mg/kg/day (PDR-NEORAL®, 1998). Therefore, if a child weighing 14 kg drank the contents of an entire vial, the dose ingested by would be 1/175 of the recommended starting dose of NEORAL®.

6.0 BENEFIT/RISK EVALUATION

Left untreated, KCS can be severe, debilitating, and sight-threatening. Complications of severe KCS include increased risk of ocular infections and corneal melting. Currently available therapies have limited usefulness. For example, topical corticosteroids are associated with well known side effects, such as increased intraocular pressure, increased risk of cataract formation, decreased wound healing, and exacerbation of infection. Neither surgical approaches, which have a risk of infection, nor palliative management alters the underlying course of dry-eye disease.

In contrast, cyclosporine ophthalmic emulsion has an excellent benefit/risk profile, making it a valuable treatment for patients with dry-eye disease. Clinical benefits of cyclosporine treatment include:

- improvement in signs and symptoms of KCS
- reduction in the ocular inflammation and immune reactivity that have been shown in several studies to be a component of the pathophysiology of KCS
- a reduction in types of organisms cultured and absence of ocular infections
- good local tolerability
- no significant systemic effects, which correlates with the observed minimal systemic exposure

Compared with these benefits, the risks associated with topical cyclosporine treatment of KCS are the common ocular adverse events associated generally with topical therapies, which include burning and stinging. Serious adverse events were reported infrequently during the clinical trials, and each was considered by the investigator to have no relationship to, or unlikely to be related to, study medication.

A brief elaboration of each of these benefits and risks follows.

Improvement of KCS signs and symptoms: In both Phase 3 studies, most individual efficacy parameters showed statistically significant improvement from baseline in each treatment group. , a significantly greater proportion of patients responded to treatment with cyclosporine ophthalmic emulsion (43% to 50%) than to treatment with vehicle (29% to 31%) in each study at month 6.

Decreases in corneal staining indicate improved corneal health, with a smoother refractive surface and a reduced risk of infection and ocular discomfort. The improvement in corneal staining can have a beneficial effect on vision as well, and subjectively, patients experienced less blurred vision. Substantial and clinically important increases in tear production (Schirmer tear test with anesthesia) were seen in both studies after 6 months of treatment with 0.05% cyclosporine emulsion. Another indicator of disease severity is the frequency of artificial tear use. After treatment with 0.05% cyclosporine emulsion for 6 months, average REFRESH® use decreased, suggesting that patients' eyes felt better.

Ocular microbiology: Ocular microbial analyses of conjunctival bacterial isolates in the Phase 2 study showed that cyclosporine emulsion treatment was associated with a decrease from baseline in the types of organisms cultured. Similar significant reductions of pathogenic organisms have been seen in dry-eye patients after punctal occlusion, suggesting that adequate tear production plays a role in the maintenance of normal ocular flora (Castillo et al, 1994). Consistent with previous animal data (Salisbury et al, 1995, study reports 1793-3936-6 and CHV-985-126), no ocular infections were reported in patients treated with cyclosporine ophthalmic emulsion in the clinical trials.

Ocular safety: The most common ocular adverse event was burning, which was more frequent with cyclosporine emulsion than vehicle in the Phase 3 studies. Other ocular adverse events reported by 1.0% (3/293) to 4.8% (14/293) of patients receiving 0.05% cyclosporine emulsion in the Phase 3 studies (in order of decreasing incidence) were discharge, foreign body sensation, conjunctival hyperemia, stinging, irritation, visual disturbance, pruritus, photophobia, dry eye, eye pain, conjunctivitis, eyelid edema, epiphora, and vitreous floaters. Adjunctive ocular safety assessments of visual acuity, intraocular pressure, and biomicroscopy showed no clinically significant differences among cyclosporine emulsion and vehicle-treated patients in the clinical studies.

Systemic safety: Consistent with the excellent safety profile in animal studies, systemic adverse events were reported at similar rates with cyclosporine ophthalmic emulsion and vehicle in the clinical trials.

In conclusion, the clear clinical benefits significantly outweigh the minimal risks associated with this treatment and cyclosporine ophthalmic emulsion thus represents a valuable treatment for patients with moderate to severe dry eye disease. This favorable risk/benefit ratio is further reinforced by the lack of satisfactory alternative therapies for these patients.

7.0 CONCLUSIONS

In summary, 0.05% cyclosporine ophthalmic emulsion is proposed for approval for the treatment of moderate to severe KCS because it has proven benefits, is at least as effective as 0.1% cyclosporine emulsion, and is safe and well tolerated. This proposal is supported by the efficacy and safety of 0.05% and 0.1% cyclosporine emulsions demonstrated in a substantial clinical program.

- In each study at month 6, analysis _____ showed that a significantly greater proportion of patients responded to treatment with cyclosporine ophthalmic emulsion (43% to 50%) than to treatment with vehicle (29% to 31%).

_____

_____

_____, statistically significant improvement favoring cyclosporine versus vehicle was found in study 002 for corneal staining ($P = 0.008$) and in study 003 for Schirmer with anesthesia ($P < 0.001$). Marginal significance favoring cyclosporine was found for Schirmer with anesthesia in study 002 ($P = 0.066$) and for REFRESH® use in study 003 ($P = 0.087$).

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- The vehicle itself provided beneficial effect to patients, as expected with a formulation designed for the dry-eye population. However, all statistically significant among-group

differences in the ITT favored cyclosporine over vehicle. This improvement is particularly important when it is recalled that the use of REFRESH® tears was permitted as needed during the clinical studies.

- Cyclosporine ophthalmic emulsion administered BID in concentrations from 0.05% to 0.4% for up to 3 months, and 0.05% and 0.1% for up to 6 months, was well tolerated locally without significant systemic effects. Topical administration produced minimal systemic exposure, which correlated with the lack of systemic toxicity found in these studies.

Thus the benefits of improvement in signs and symptoms of dry eye and reduction in ocular surface inflammation seen with cyclosporine ophthalmic emulsion outweigh the minimal risks associated with this treatment. Cyclosporine ophthalmic emulsion represents a valuable treatment for patients with moderate to severe dry eye disease. It is recommended for patients with chronic KCS: patients with a confirmed diagnosis of KCS that is inadequately controlled by conventional palliatives such as artificial tears and ointments.

8.0 REFERENCES

8.1 STUDY REPORT REFERENCES

STUDY NO. STUDY TITLE

STUDY NO.	STUDY TITLE
NADA 141-052	Freedom of Information Summary of New Animal Drug Application (NADA) 141-052, August 1995.

STUDY NO. STUDY TITLE

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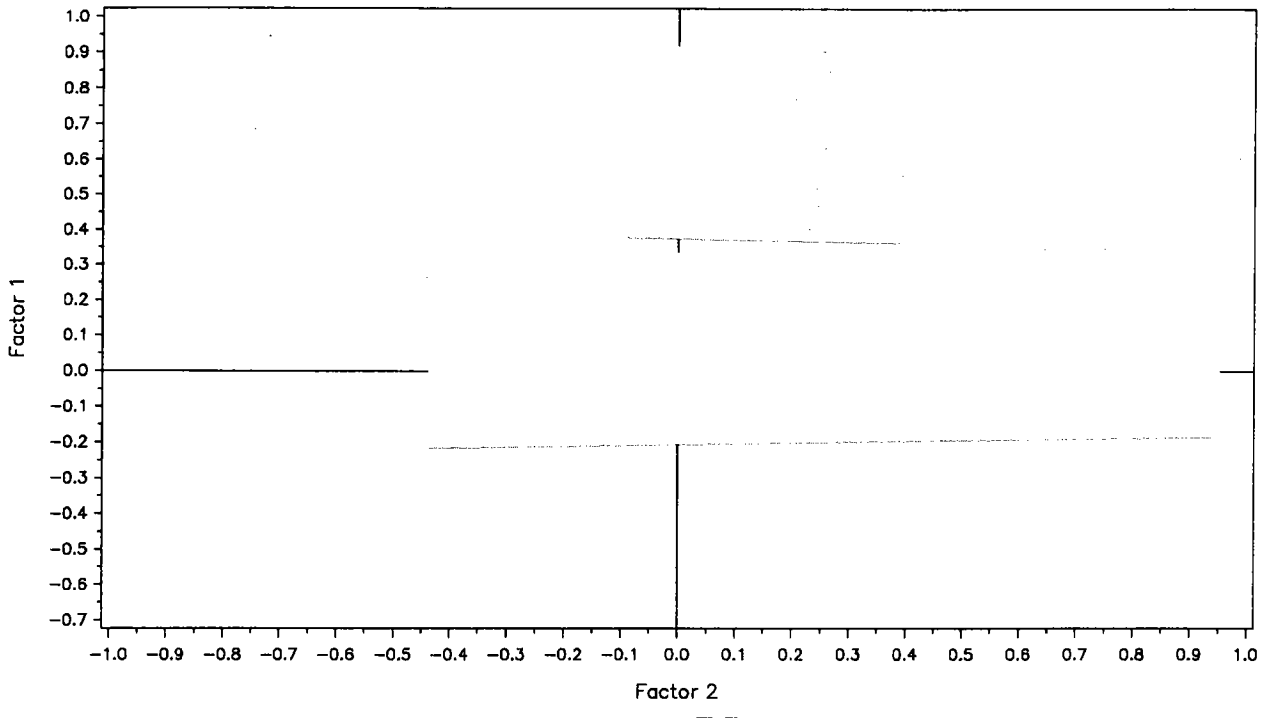
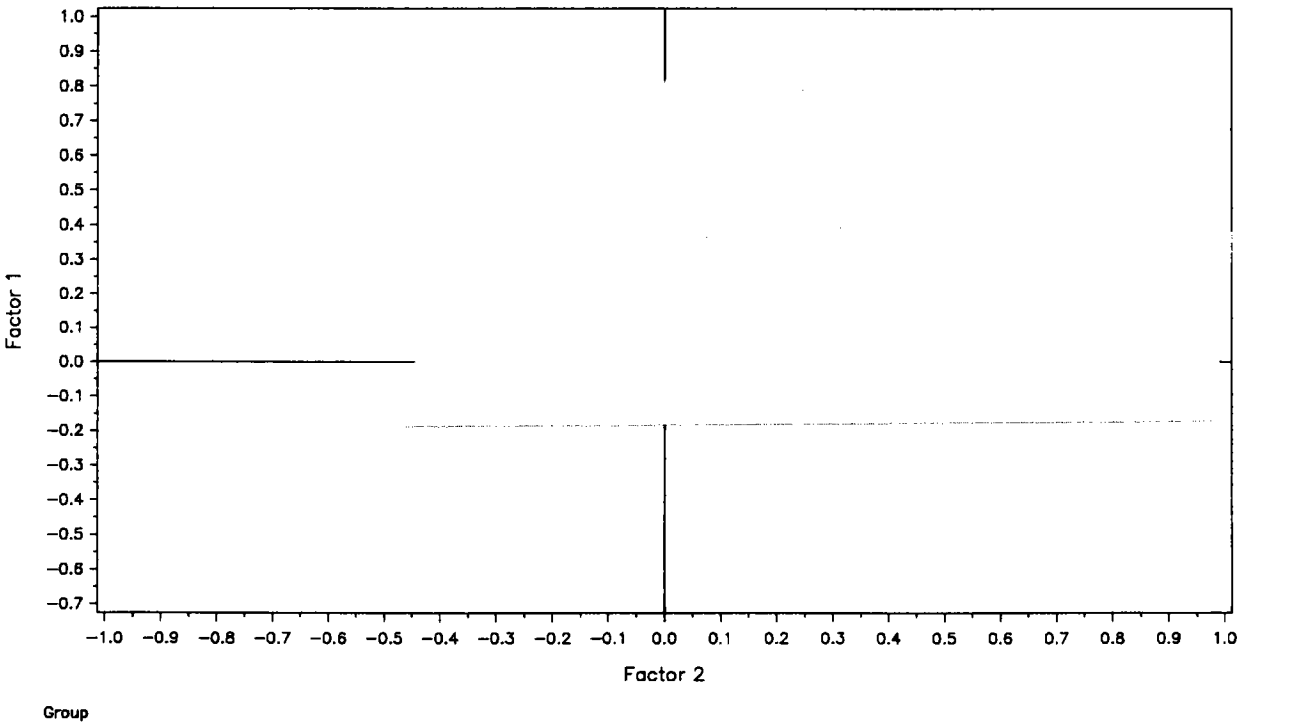
9.0 FIGURES

Study 002 FIGURE 1 (Intent-to-Treat)
Baseline Factor Analysis



/bostat/rozin_ri/192371002/month6/csa2e264.sas / 14JUN99

Study 003 FIGURE 2 (Intent-to-Treat)
Baseline Factor Analysis



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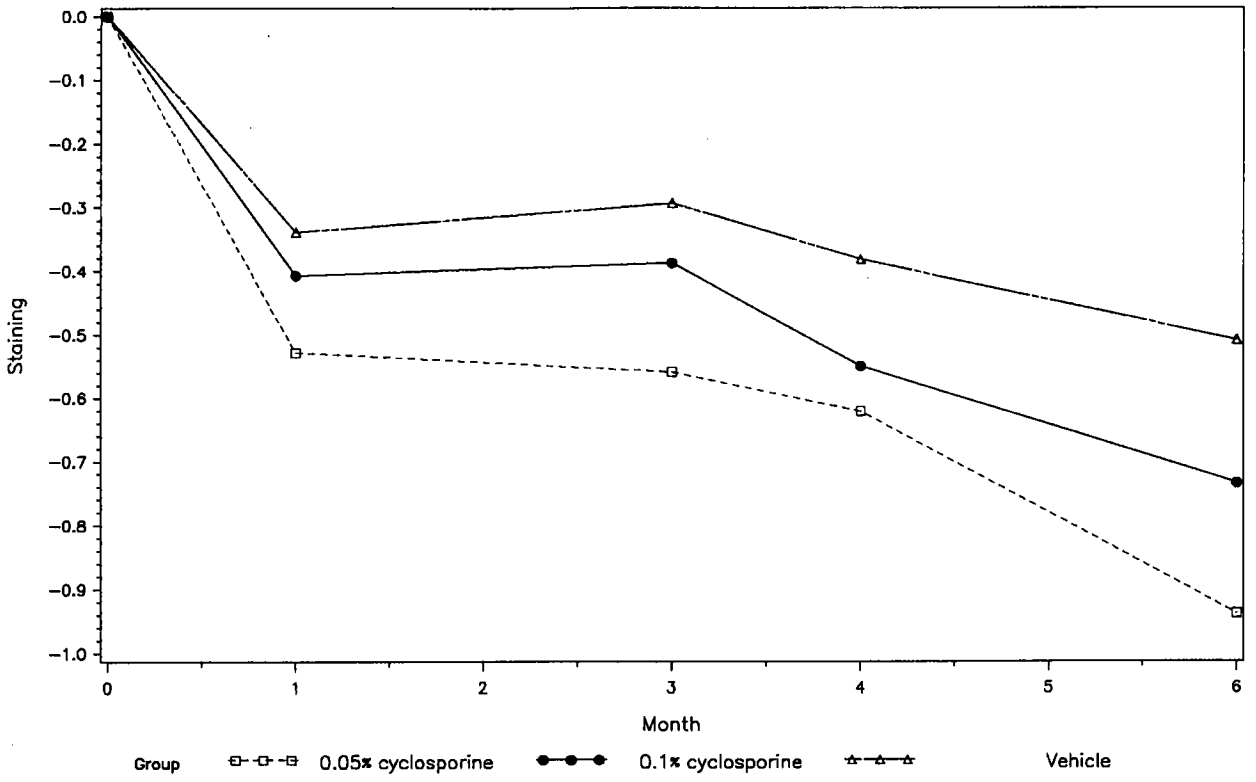
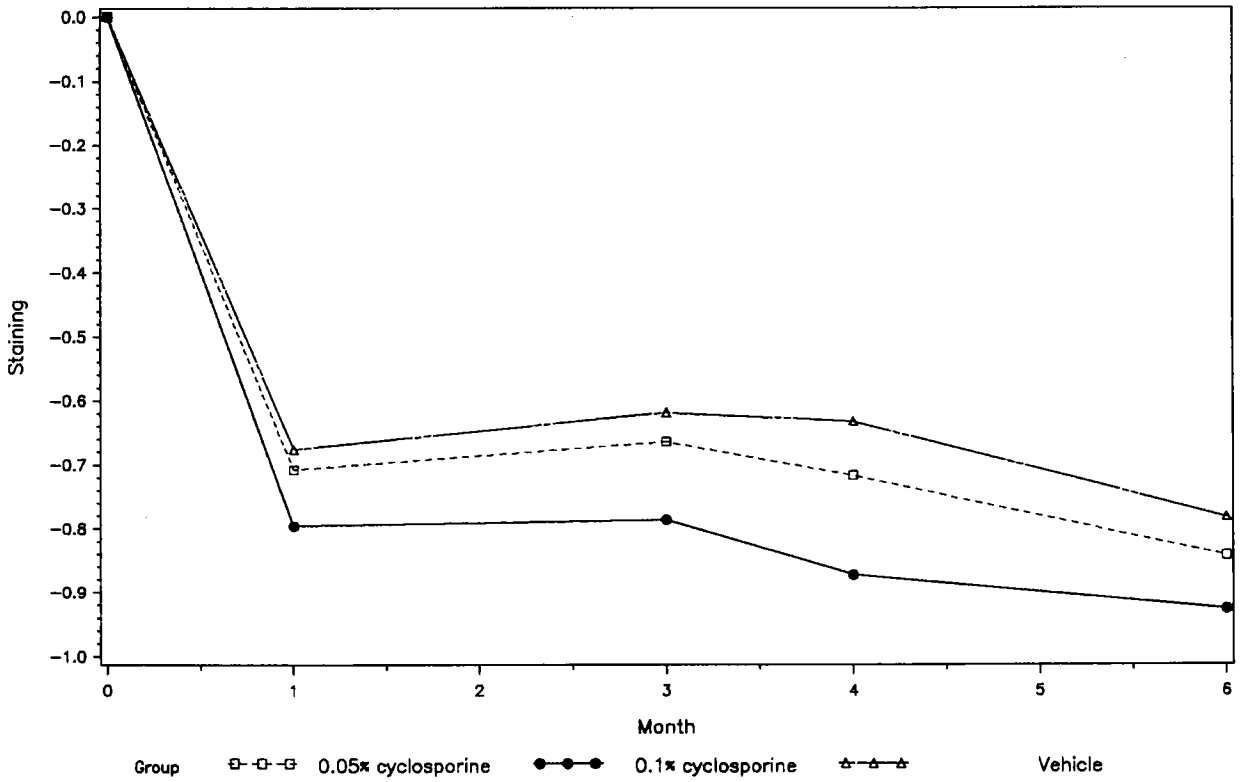
Study 002 FIGURE 5 (Intent-to-Treat)
Corneal Staining [a]: Change from Baseline



[a] Corneal Staining on a 6-point severity scale (0 to 5) using worse eye. A negative change from baseline indicates improvement.
Note: At month 6, 0.05% cyclosporine is significantly better than vehicle (p=0.002).
/bostat/rozin_ri/192371002/month6/csa2e260.sas / 14JUN99

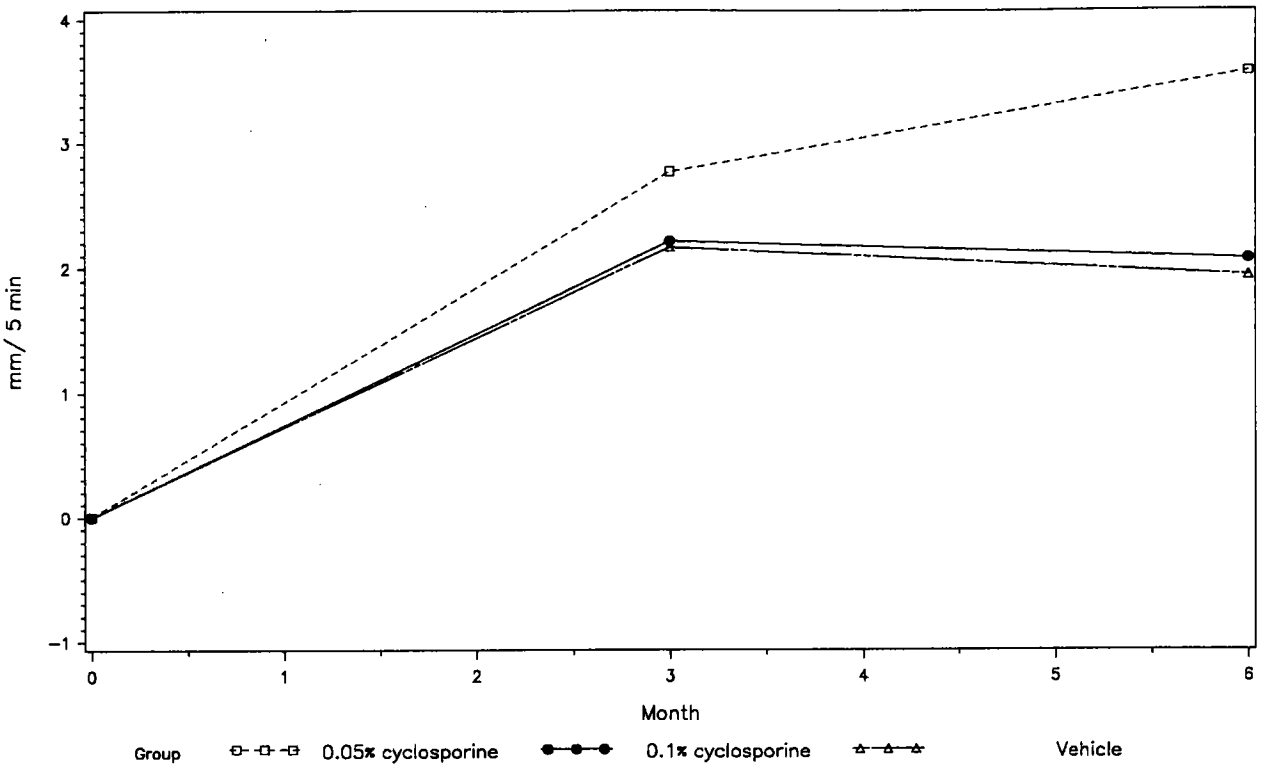
Study 003 FIGURE 6 (Intent-to-Treat)
Corneal Staining [a]: Change from Baseline



[a] Corneal Staining on a 6-point severity scale (0 to 5) using worse eye. A negative change from baseline indicates improvement.

/bostat/rozin_ri/192371003/month6/csa3e265.sas / 14JUN99

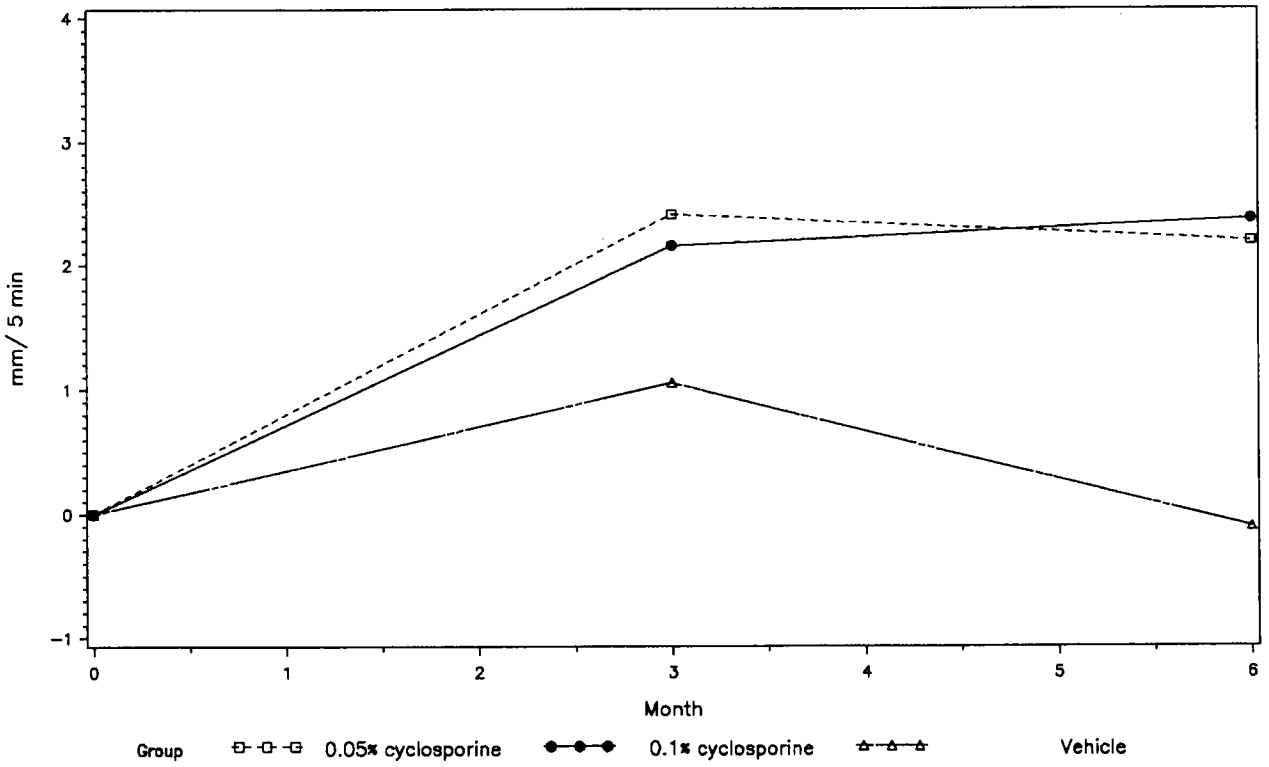
Study 002 FIGURE 7 (Intent–to–Treat)
Schirmer Values (with anesthesia)[a]: Change from Baseline



[a] Schirmer values in mm/ 5 min using worse eye. A positive change from baseline indicates improvement.

/bostat/rozin_ri/192371002/month6/csa2e261.sas / 14JUN99

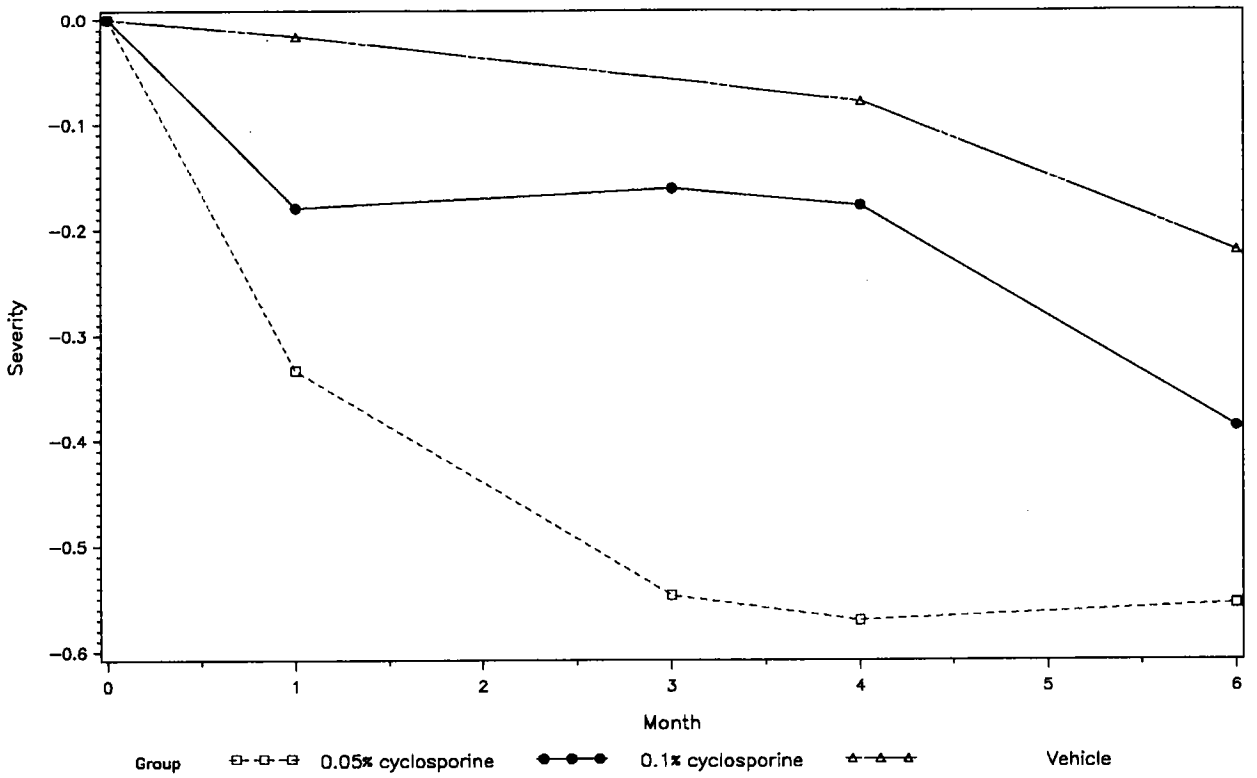
Study 003 FIGURE 8 (Intent–to–Treat)
Schirmer Values (with anesthesia)[a]: Change from Baseline



[a] Schirmer values in mm/ 5 min using worse eye. A positive change from baseline indicates improvement.
Note: At month 6, both 0.05% and 0.1% cyclosporine are significantly better than vehicle (p=0.001).

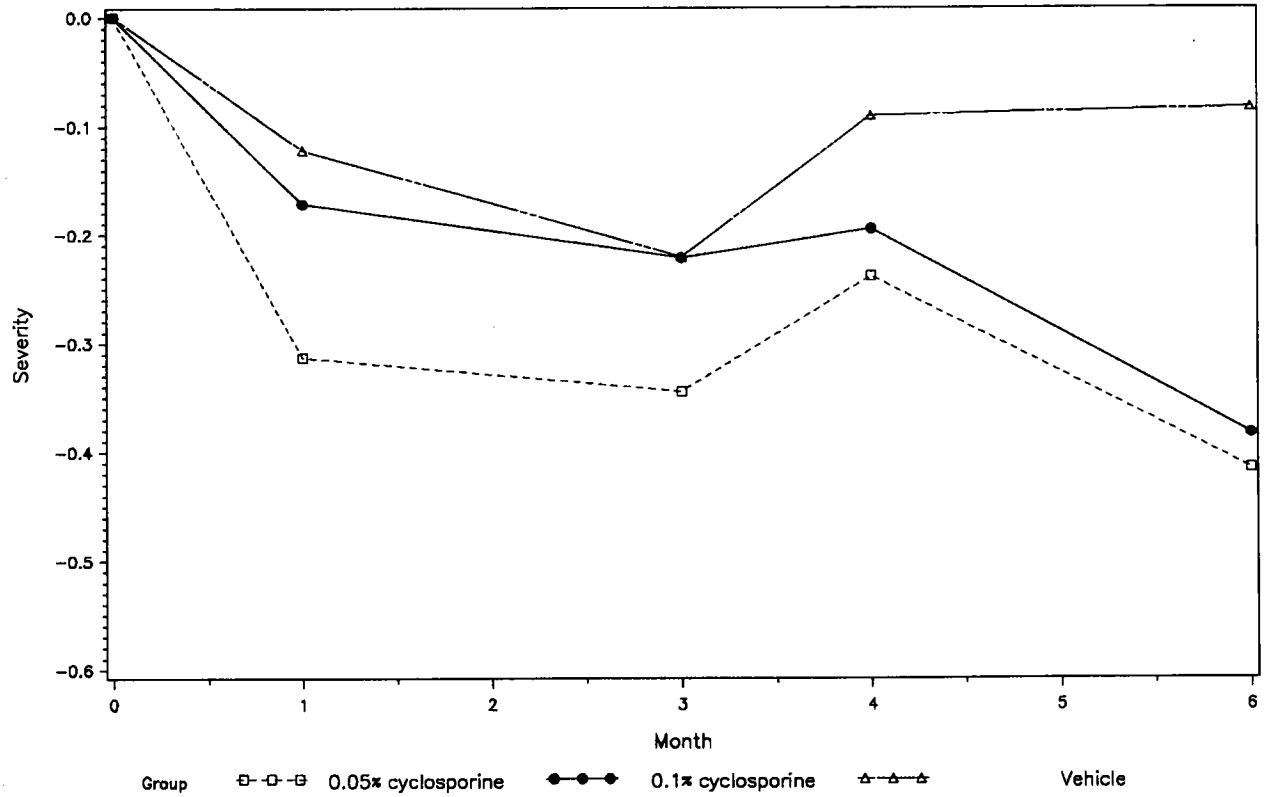
/bostat/rozin_ri/192371003/month6/csa3e266.sas / 14JUN99

Study 002 FIGURE 9 (Intent-to-Treat)
Blurred Vision Severity [a]: Change from Baseline



[a] Blurred vision on a 0 (do not have symptom) to 4 (always notice this symptom) scale. A negative change from baseline indicates improvement.
Note: At months 3 and 4, both levels of cyclosporine are significantly better than vehicle ($p<0.02$).
/bostat/rozin_ri/192371002/month6/csa2e262.sas / 14JUN99

Study 003 FIGURE 10 (Intent-to-Treat)
Blurred Vision Severity [a]: Change from Baseline

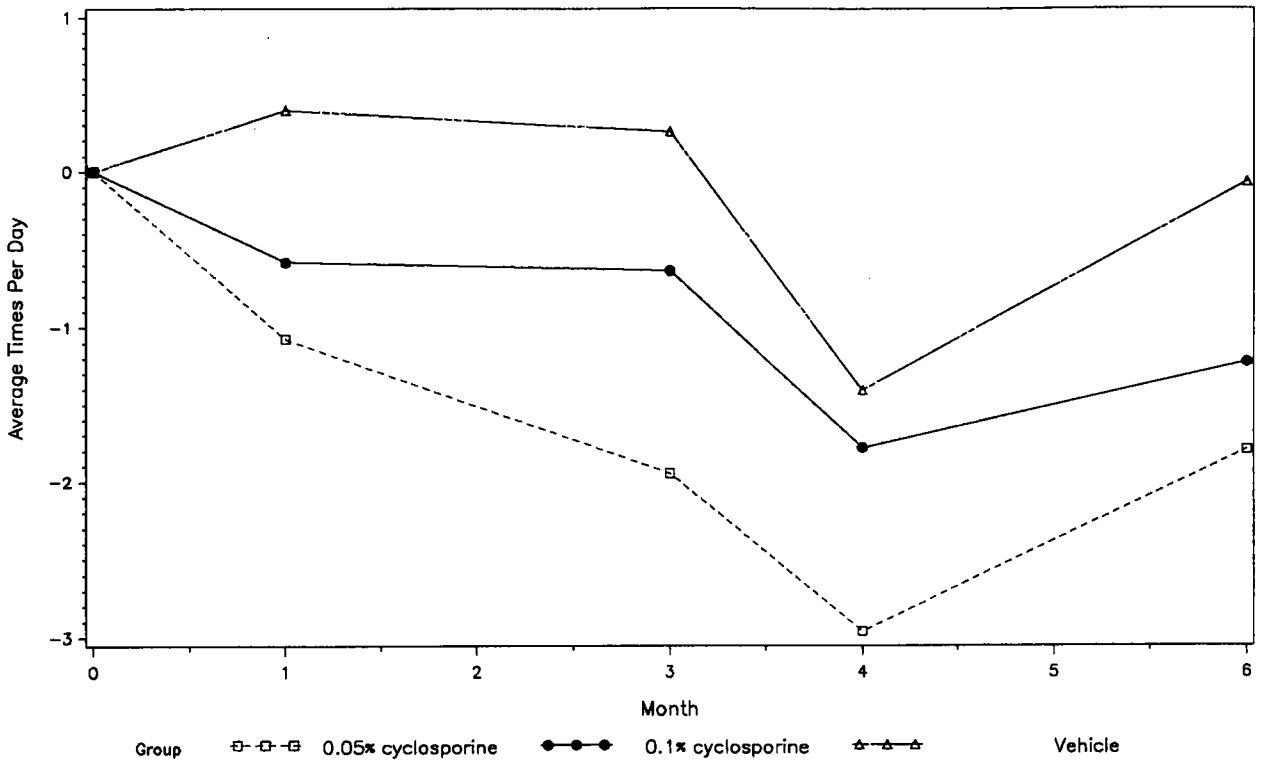


[a] Blurred vision on a 0 (do not have symptom) to 4 (always notice this symptom) scale. A negative change from baseline indicates improvement.

/bostat/rozin_ri/192371003/month6/csa3e267.sas / 14JUN99

Study 002 FIGURE 11 (Intent-to-Treat)

Patient Responses: Average Daily Refresh(R) Use During the Previous Week [a]: Change from Baseline



[a] Patient estimated times per day that Refresh(R) was used during the past week

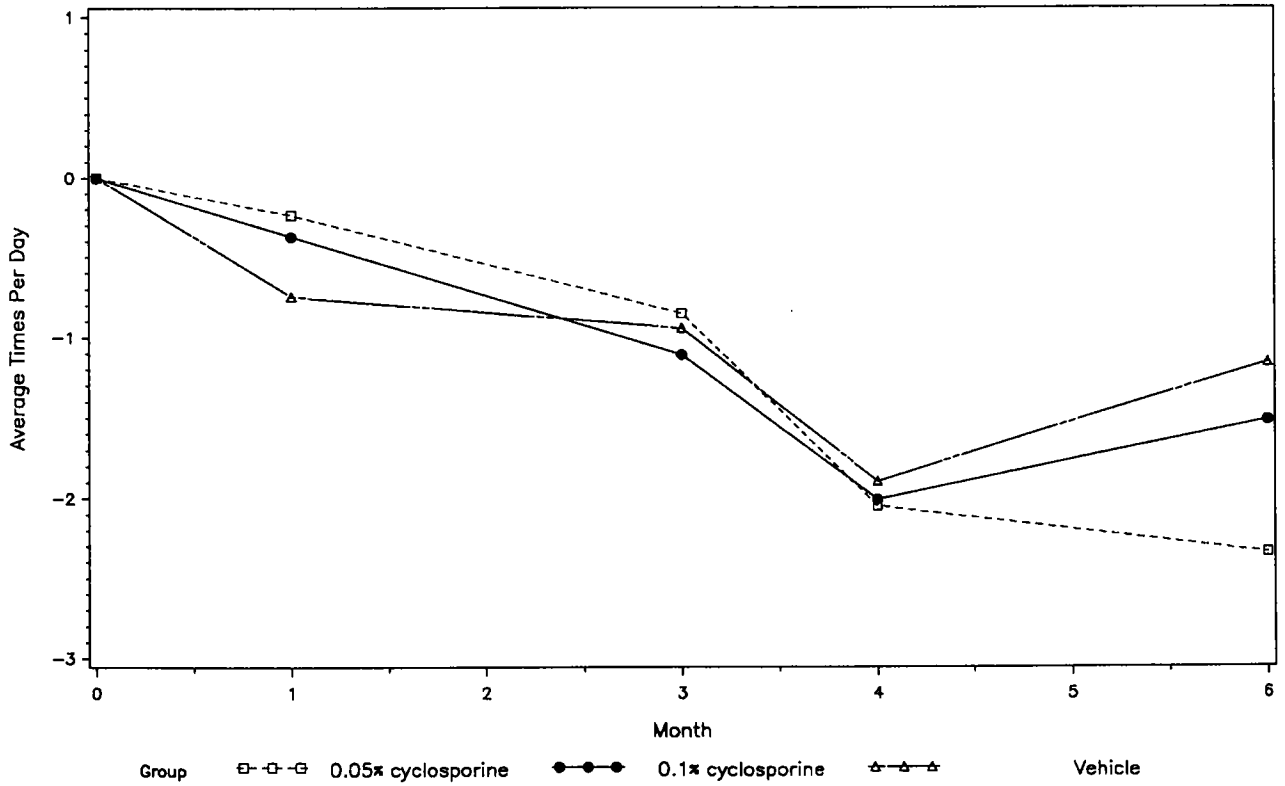
negative change from baseline indicates improvement.

Note: At month 3, 0.05% cyclosporine is significantly better than vehicle (p=0.017).

/bostat/rozin_ri/192371002/month6/csa2e263.sas / 14JUN99

Study 003 FIGURE 12 (Intent-to-Treat)

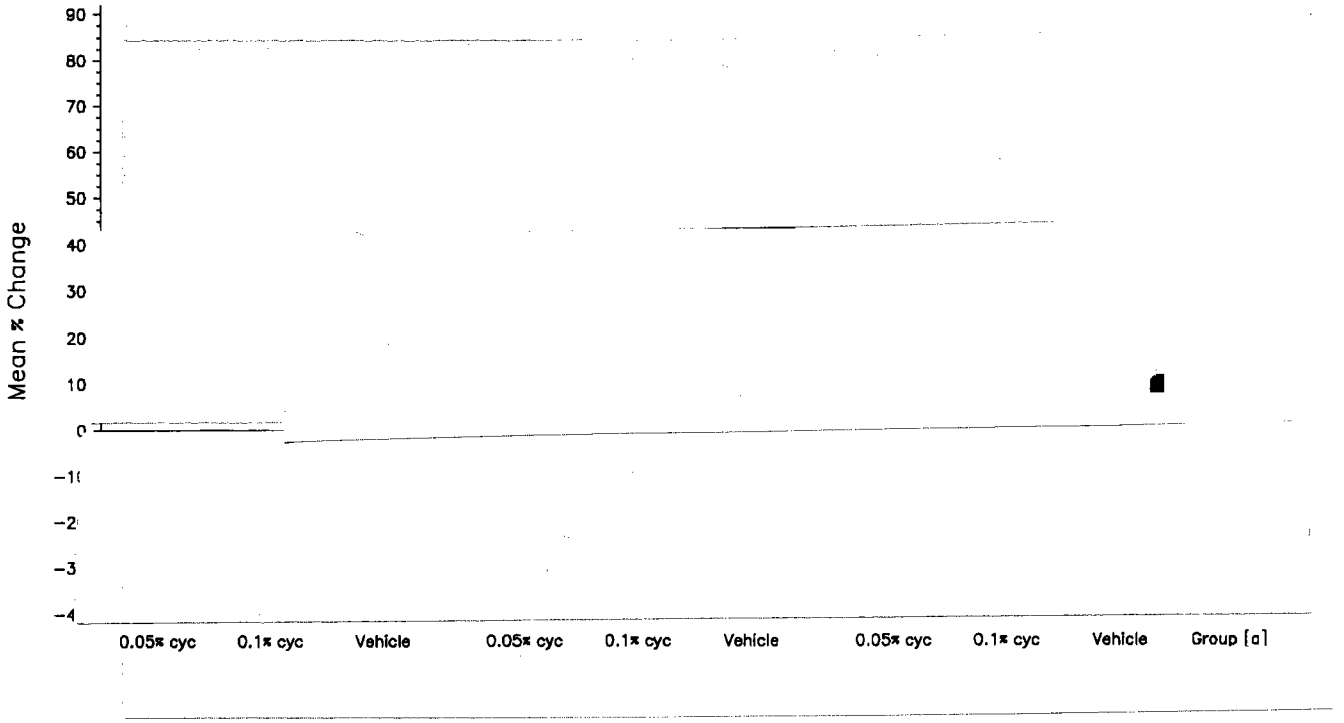
Patient Responses: Average Daily Refresh(R) Use During the Previous Week [a]: Change from Baseline



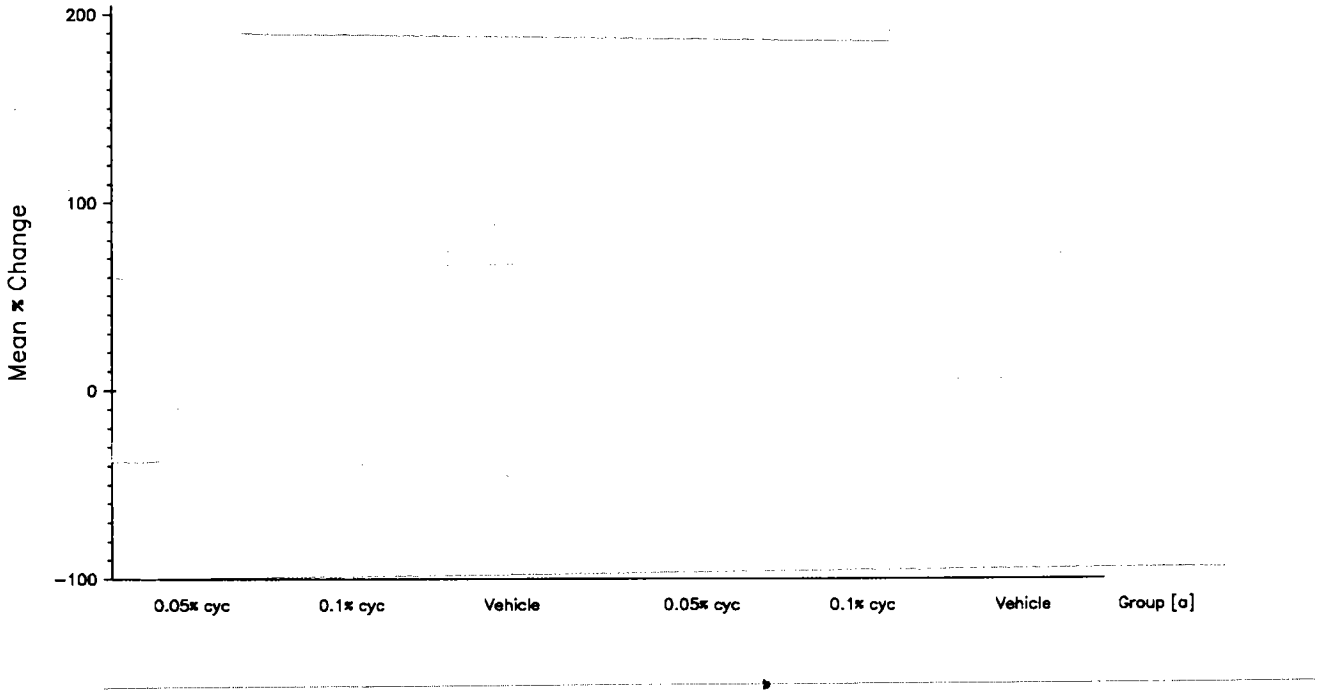
[a] Patient estimated times per day that Refresh(R) was used during the past week

negative change from baseline indicates improvement.

/bostat/rozin_ri/192371003/month6/csa3e268.sas / 14JUN99



Note: A negative change from baseline indicates improvement.
Sample sizes for the 3 treatment groups: 0.05% cyc (N=13), 0.1% cyc (N=6), Vehicle (N=13).
/bostat/rozin_ri/192371/tertiary/csate217.sas / 14JUN99



Note: For HLA-DR at month 6, 0.05% cyclosporine is significantly better than vehicle (p=0.018). A negative change from baseline indicates improvement.
Sample sizes for CD11a: 0.05% cyc (N=13), 0.1% cyc (N=6), Vehicle (N=13).
Sample sizes for HLA-DR: 0.05% cyc (N=13), 0.1% cyc (N=4), Vehicle (N=12).

/bostat/rozin_ri/192371/tertiary/csate218.sas / 14JUN99